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APRIL 24, 1953

VOLUME 117 NUMBER 3043

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BECAUSE of the number of articles submitted for publication in SCIENCE, and because of the considerable length of many papers, the editors find it increasingly difficult to keep from falling farther and farther behind in the schedule of publication. In order to assure publication of new work with a minimum of delay, and in order to provide a much wider range of interest in each issue of SCIENCE, the Editorial Board announces the following change in policy:

1. Only under exceptional circumstances, such as suitability for a lead article, will any technical paper of more than four manuscript pages, double spaced (ca. 1200 words), be accepted. This includes space occupied by references, figures, and tables. *Most papers should be limited to 900 words.* This does not mean that abstracts which state conclusions without supporting data will be acceptable. *Supporting data should be included to the extent necessary,* particularly in the form of concise tables.

2. Once the accumulated manuscripts have been published, every effort will be made to publish technical papers within ten weeks of receipt. This will require the cooperation of authors, first in respect to conciseness and brevity of expression; second, in careful attention to the standard forms used in SCIENCE for references, abbreviations, legends to figures, headings of tables, etc.; and third, in prompt correction and return of proofs.

3. Every manuscript must be submitted in duplicate in order to expedite editorial handling. In case of return to authors, one copy will be retained in the Editorial Office pending final disposition.

4. Lead articles of greater length (up to 10,000 words) are invited for consideration. These may be general articles or reviews of recent advances in some field. Writers of such articles should keep in mind the broad audience of SCIENCE and should write in sufficiently non-technical terms to be intelligible to a general scientific audience.

THE EDITORIAL BOARD

SCIENCE, founded in 1880, is published each Friday by the American Association for the Advancement of Science at the Business Press, 10 McGovern Ave., Lancaster, Pa. Entered as second-class matter at the Post Office at Lancaster, Pa., January 13, 1948, under the Act of March 3, 1879. Acceptance for mailing at the special rate postage provided for in the Act of February 28, 1925, embodied in Paragraph (d-2) Section 34.40 P. L. & R. of 1948.

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# *Publications Received*

***The Bacteriostatic Activity of 3500 Organic Compounds for Mycobacterium Tuberculosis Var. Hominis.*** Chemical-Biological Coordination Center, Review No. 4. Guy P. Youmans, Leonard Doub, and Anne S. Youmans. Washington, D. C.: National Research Council, 1953. 713 pp. $5.00.

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***Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water.*** Handbook 52. National Bureau of Standards. Washington, D. C.: GPO, 1953. 45 pp. 20¢.

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***An Unsolved Problem of Biology.*** An Inaugural Lecture. P. B. Medawar. London: University College, 1952. 24 pp. 5s.

# A Reconsideration of the Somatic Mutation Theory of Cancer in the Light of Some Recent Developments

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IN THE STUDY OF ONCOLOGY, one is occasionally induced by obstinate manifestations of cellular anarchy to reconsider what has been, since the time of von Hansemann and Boveri, the much-debated somatic mutation theory of cancer. Since recent experimental investigations have served to renew interest in the theory, one may hope that the theory will be divorced from the *reductio ad absurdum* to which it was once relegated. In a discussion on the nature of gene action, Beadle (*1*) seems to have accounted correctly for the disfavor in which the somatic mutation theory has fallen when he stated that "Possibly one reason why this theory has been looked on with so little favor in certain quarters is that it offers little hope for a cancer cure." It should not be assumed that, if the somatic mutation theory be proved valid, all hope for a cancer cure automatically evaporates.

Recognizing the multiplicity of characters and characteristics that have been shown to be under the control of the genetic constitution of the organism, it is by no means unreasonable to suppose that certain genes also play a prominent role in the direct or indirect initiation and control of cell division in morphogenesis and in reconstitution. The morphology and physiology of a particular organ are the result of the interaction of a multitude of genes. In the development of a structure that is to perform a particular function, there must exist a condition that will assure thousands of cell divisions in predetermined orientation and time schedule to bring about the necessary macroscopic and microscopic differentiation.

Hammett (*2*), who has studied the effect of chemical stimulators on developmental growth, expressed it in these words:

> The ordered production of a species-true organism is the property of heredity. Thus the species specificity in chemical composition, and the superimposed specificity in organ and tissue composition are determined through heredity. Heredity also sets the species, organ, tissue, and cellular specific course of development. Heredity thus selects the characterizing chemical building materials of the developing organism. [Concerning cancer, he continued] . . . the course of development and the distinctive chemical nature of cancer and cancer cells is set by heredity. . . . The fact that cancer cells proliferate true to type, and form other cancer cells through many generations is sufficient evidence for the foregoing dictum.

Cells, whether germinal or somatic, which have been exposed to agencies capable of producing mutations, frequently reflect the effect of the adverse environmental state by giving rise to an anomaly, the persistence of which in the species depends upon the degree of undesirable deviation from the normal, and whether the mutation took place in the germinal or somatic cells.

Many attempts have been made in the past to establish a relationship between the neoplastic cell and chromosomal aberrations. Some have held that there exists a preponderance of aberrant chromosomes in malignant cells. Others have either doubted this or have maintained that such anomalies are not necessarily restricted to the cancer cell. It might also be pointed out that the morphologic alterations observed in *in vitro* cultures of mouse fibroblasts could not be correlated with the sarcomatous transformations of the cells (*3, 4*).

Speculating on the possibility of cancer being the result of a somatic mutation, Morgan and Bridges (*5*) gave a brief résumé of Boveri's cancer theory. Boveri suggested that cancer might result as a consequence of imperfect or irregular division of the chromosomal complex. The abnormal distribution of chromosomes might cause a loss of the factors which normally inhibit the rate of cell growth. However, as pointed out by Morgan and Bridges, such chromosomal aberrations are not necessarily associated with cancer growth. They conceive it to be quite possible that cancer may be due to a recurrent somatic mutation of some gene. In their concluding remarks, the authors feel that it should be kept in view ". . . that what is inherited in cancer may be a gene or complex of genes in which somatic mutation is of sufficient frequency to give the appearance that a gene for cancer is itself inheritable."

Koller (*6*) investigating the cytology of various human tumors, found that the number of chromosomes had a range of 12–48, with a frequency peak at about 30 and another but lower peak at 45 chromosomes. Abnormalities such as stickiness, suppression of spindle, and irregular or polyploid chromosome numbers were in part attributed to a scarcity of food supply and toxic breakdown products.

In cytologic studies of human normal somatic tissues (proliferative stages of the adult uterine epithelium and embryonic tissues), Timonen and Therman (*7*)

and Therman and Timonen (*8*) found that the chromosome number varied considerably, and that the number 48, generally held to be a constant, is *not* the most common outside of the germ line.

Koller (*9*) carried out cytological analysis on some 565 human carcinomas obtained from various organs and tissues and reported that tumors were found in which most of the cell divisions took place through normal mitosis. In some tumors, however, a large proportion of the cells was found to undergo abnormal mitosis. According to Koller, the fundamental cause of increased division rate and malignancy is the excess amount of nucleic acid present in the tumor tissue, and he suggests that it is not improbable that the initial change in nucleic acid metabolism is brought about in the final analysis by a gene mutation which may be assumed to have occurred in the region controlling nucleic acid supply either directly or indirectly.

As the result of his work on tumor transplantability and immunity, Tyzzer (*10*) concludes:

> From the evidence in the biological character of tumors of a permanent modification of somatic tissue, it appears logical to regard a tumor as a manifestation of *somatic mutation*. As a basis for this, there may be modification in the relative value either by loss or addition, or in the nature of factors, any of which, if continuously transmitted thereafter in successive cell generations will constitute a type of mutation. This, unlike the mutations which may affect the germ plasm, is maintained only through artificial transplantation from one individual to another. The tissue of a new growth has thus in certain respects become foreign to the other tissues. Its growth is no longer controlled by the normal inhibiting influences which constitute a regulating mechanism, but it behaves more or less as a parasite living at the expense of its host; and it may excite a reaction of the surrounding tissue which is in some cases more favorable, in other cases less favorable, to its continued growth. Malignant tumors must have feeble antigenic power as well as sufficient resistance to the normal inhibiting influences to provide for continued growth in the animal in which they originate, otherwise reactions sufficient to destroy them would occur more frequently.

Before presenting experimental evidence in support of the somatic mutation theory of cancer it might be well, at least provisionally, to define the theory as follows:

I. A point or regional mutation affecting one or more genes, which directly or indirectly is responsible for the initiation and continuation of an indeterminate number of cell divisions.

II. This type of specific mutation need not necessarily involve a chromosomal aberration or any other kind of visible nuclear change.

III. Cells so mutated may or may not show incomplete differentiation (depending, perhaps, on division rate).

IV. Other mutant characters may be associated with the cell-division factor, the frequency of such occurrence being dependent upon the relative mutagenic susceptibility of other genes. Such an associated mutation may, for example, reveal itself as an alteration in its transplantation pattern, with or without a corresponding change in its antigenic properties.

The process that causes unlimited cell division in cancer is of a different nature than that encountered in ordinary regeneration or wound repair. In the latter case an injury calls forth certain "intercellular wound hormones" capable of inducing cell division. When the repair process is completed the stimulating substances may be said to be depleted, or there follows a restoration of equilibrium between growth stimulators and depressors. Thus the activity of the division factor or gene in wound repair or cell replacement is subservient to the intercellular hormones and therefore fulfills its obligation toward the normal maintenance of the organism. In the case of a neoplasm, however, it appears that an injury of a *specific nature* is required, which in some way either alters (mutates) the division factor so as to give it unrestricted expression, or destroys or mutates a division-inhibiting factor. The division mechanism has lost all restraint in the cancer cell, it flouts (within physiological limits) the systemic regulatory agents. One might say it has acquired an introverted individuality, which it tenaciously retains even though transplanted into relatively compatible hosts through many generations. That the change is of a permanent nature and not influenced by the systemic factors of the host has been demonstrated *in vitro*, where it was found that tumor cells of the mouse (*11*) and of the rat (*12–14*) could be maintained in culture for an indefinite period without losing their malignant characteristics.

There may also be concomitant secondary characteristics in the malignant cell, such as chromosomal aberrations, delimited differentiation, and changes in salt content and in enzymatic and glycolytic activity. These might well be by-products, so to speak, of abnormally proliferating adult tissue cells, or in some particular cases where any one of these factors deviates considerably from the general trend, it may be an associated mutation or response to an environmental change. This may be an audacious supposition, but the fact remains that the one principal character of a neoplasm is unlimited cell division, and that in no case yet observed has it been demonstrated that cell division is the effect, and not the cause, of any of the above-mentioned metabolic and cytologic abnormalities.

The persistent number of cell divisions that characterize a cancer is the one unequivocal feature which, above all, lends credence to the somatic mutation theory. Once abnormal division rate is initiated it continues, the process being an irreversible reaction. Gene reversions probably occur occasionally, as in the germinal cells, but at the most one or a few cells within the mass of malignant tissue may undergo such a change, and, needless to say, such a reversion is of little consequence. Although an exceedingly rare occurrence, spontaneous cancers have been known to regress completely. Woglom (*15*), for example, found that among 2000 mice bearing spontaneous tumors, 13 regressed and 3 fluctuated or remained stationary. This frequency of spontaneous regression (0.8 per cent) is very much higher than that observed in man.

Rohdenburg (*16*) cites Bashford, who estimated that

spontaneous regression in man takes place about once in a hundred thousand, at 0.001 per cent. Even in such a low frequency of regressions, it would appear to be the quintessence of folly to postulate that a gene reversion takes place in such cases which simultaneously affects all the malignant cells composing the tumor. Indeed, regression of a neoplasm requires something other than a reversion to the normal type of cell. It does not necessarily follow that, if cancer is the result of a somatic mutation, no environmental change could be instrumental in bringing about a recession. That regressions, both spontaneous and induced, do occur even in a relatively small percentage of cases, is fortunately the greatest incentive for continued research. Environmental modifications of certain mutant characters are not unknown. For example, in *Drosophila* (*17*), the mutant character *vestigial wing* is a greatly reduced wing size if the flies are raised at one temperature; however, if they are grown at another temperature, the size of the wing approaches that of the normal wild type. A more striking example (*18*), and more pertinent to the problem at hand, is the conditioning effect of the so-called extrachromosomal or milk factor on the percentage of spontaneous mammary cancers in highly inbred mice. In the A strain mice, which are so constituted genetically that about 84 per cent of the females develop spontaneous breast cancers, only 8 per cent develop the cancer if foster-nursed by females of a low breast cancer incidence (C57 black strain).

Mice that have been selectively inbred for many generations to produce a high and low spontaneous tumor incidence have demonstrated that predisposition to cancer, at least in certain tissues, is to a large extent dependent on the genetic constitution.

Man himself furnishes sufficient evidence of cancer predisposition. The high rate of cancer of the uterus and breast in the female, and of the stomach, colon, rectum, and prostate in the male, compared to other organs and tissues is quite significant. The appearance of tumors in human monozygous twins furnishes some rather substantial evidence of genetic predisposition to cancer. In an analysis of tumor development in monozygous and dizygous twins, Macklin (*19*) studied some hundred cases and concluded that tumors appeared in both members of a monozygous twin pair far more frequently than they do in both members of a dizygous twin pair. Tumors of the same type, in the same organ, and occurring at the same time in both members of the pair, were significantly higher in the monozygous than in the dizygous twins.

Phenotypic expression is frequently dependent on certain combinations of interacting or modifying genes. It has been shown, for example, that stable genes can become unstable in the presence of a certain nonallelic gene (*20*). In studying the rate of spontaneous mutations in Drosophila collected from various parts of the world, Demerec (*21*) found that the frequency of spontaneous lethals in the X-chromosome was much higher in a strain from Florida than in other strains. Analysis showed that this higher rate was due to the presence of a recessive gene in the second chromosome. Not only does this gene produce a high frequency of lethals, but it also increases the rate of visible mutations controlled by a number of other genes.

Another illustration of the behavior of an unstable gene is given by Demerec (*22*) in the case of a race of delphiniums. Purple spots on a rose background on the flowers of the rose-variegated delphinium are interpreted as due to changes in the rose gene from rose into its purple allele. Each of these purple spots is the result of a change which took place sometime during the development of the flower. If the change occurs early in development, the cell with the changed gene will divide many times, and therefore produce a large spot; a smaller spot will be produced if the change occurs late in development. The size of the spots therefore indicates the time in ontogeny when the change occurred, and the number of spots is a function of the frequency of changes. From seeds of a self-pollinated variegated plant, a few purple plants are obtained in addition to variegated offspring. These purple plants are the result of a mutation or change of the gene for rose into the gene for purple affecting the germ cells. Similar somatic mutations have been brought about by x-rays in the color of the developing eye of *Drosophila melanogaster* (*23*).

In a discussion on the induction of mutations by carcinogens, Strong (*24*) expressed two aspects of the genetic problem in relation to cancer origin:

> I—susceptibility and resistance to spontaneous, transplanted, and induced tumors—an inherited constitutional state or states in which the germ plasm is definitely involved, and II—the origin of neoplastic lesion by a conversion, somehow or other, from a pre-existing normal somatic tissue—a somatic mutation. The actual process of somatic mutation may either be conditioned or under the control of an inherited or germinal influence, or entirely independent of such intrinsic determination.

Experimental evidence recently accumulated tends to support the generalization of Strong (*24*) that "all mutagens are carcinogens and all carcinogens are mutagens." Thus, in 1945, Strong (*25*) injected mice subcutaneously with methylcholanthrene, and from their untreated descendants obtained 13 mutations involving coat color, thereby showing that germinal mutations could be induced with the carcinogen and at a frequency greater than could be expected by chance alone. In nontreated mice observed over a period of 27 years, the coat color mutation rate was found to be approximately 1 in 26,000. Seven of the induced mutations were repetitions of characters present in the author's stock of mice, and 6 proved to be new ones never observed previous to the methylcholanthrene injection. Two mutants other than coat color (precocious sexual activity and large first litters) were observed in another experiment in which the progenitors were treated with methylcholanthrene (*26*). Strong concluded that ". . . there is evidence the methylcholanthrene has affected the germ plasm by bringing about germinal or point mutations and per-

haps other undetermined effects. It is highly probable, therefore, that methylcholanthrene may also bring about malignancies in tissues by causing mutations to arise in them."

Carr (*27*) produced germinal mutations in mice using a subcutaneous injection of 1 : 2 : 5 : 6-dibenzanthracene. Eighty-three mice, selected from three inbred lines, were treated, and of the thousands raised, no phenotypically detectable spontaneous mutations were observed. Of the 83 mice treated, 7 mutants were found among the $F_3$ and $F_4$ offspring, a number far above the expectation where x-rays were used as a source of mutation production. Carr suggested the following argument in support of the observed facts:

> Radiation mutations are almost entirely random, i.e., if a certain gene is mutated by an ionization in one sperm, the chance that the same gene will mutate in another sperm in the same or another individual is not increased. The efficiency of mutation with regard to any given gene is thus almost zero. But this is not necessarily the case with chemicals. If a chemical distributed via the blood stream reacts with a given locus to produce a mutation in one sperm, it is obviously liable to do the same with all other similar loci in other sperms (or ova). An efficiency of mutation at a given locus at 100 per cent can thus be imagined, and then all offspring of an exposed individual will carry the abnormal gene.

In conclusion, Carr states that the types of mutants produced are somewhat different from those produced by high-energy radiations. The hydrocarbons may thus only produce mutations in genes that are less stable than others. This would result in some degree of specificity as required above, suggesting that genes whose unstable nature leads to spontaneous mutation are most readily affected.

Using mustard gas as a mutagen, Auerbach (*28*) found the rate of sex-linked lethals in Drosophila to increase from a normal of 0.2 per cent to over 7 per cent. Mosaics occur in less than 15 per cent in flies treated with x-rays, whereas flies treated with mustard gas produced about 30–50 per cent mosaics. Auerbach's experimental investigations on the various effects of mustard gas on the gene led her to suspect that the treatment does not invariably produce sudden complete mutation, but a tendency to mutate may be acquired which remains latent until a later cell division.

The mutagenicity of carcinogenic compounds was also investigated by Demerec (*29*) who, using aerosolized 1 : 2 : 5 : 6-dibenzanthracene, was able to induce X-chromosome lethals and chromosomal aberrations in Drosophila. The proportion of chromosomal inversions appeared to be higher than obtained in experiments with x-rays. In a later paper (*30*), he showed that of 7 carcinogens tested on Drosophila, 6 were found to be mutagenic. Of 9 noncarcinogens, only two were observed to be mutagens. The available evidence suggested that some chemicals (dibenzanthracene, benzpyrene, and hydroxyazobenzene) induce both gene changes (lethals) and chromosomal aberrations, whereas others (benzanthracene, dimethylaminoazobenzene, and 2-amino-5-azobenzene) are more effective in inducing chromosomal aberrations. Demerec concludes from his experiments that it seems reasonable to infer a common causative mechanism relating mutagenicity and carcinogenicity, and, "Consequently, if cancer originates through a genetic change, our chances of finding ways to prevent it are very, very slight."

That associated changes of a mutational character may occasionally accompany, or at some time follow, a mutation which is specifically concerned with unlimited cell division, has been discovered and critically studied by various workers. Thus experiments on the genetics of tumor transplantability in inbred strains of mice have demonstrated some interesting changes that can occur in the mechanism of tissue compatibility.

A spontaneous carcinoma, designated as the dBrC, arose in the highly inbred dba strain of mice (*31*). Hybrids ($F_2$) obtained by crossing the dba with Bagg albino (resistant to the dBrC tumor) produced a ratio of 1 susceptible to 4.4 refractory to the tumor. This observed ratio was close to the expected ratio of 1 : 4.61, which indicated the simultaneous presence of 6 dominant factors for the successful transplantation of the tumor. In the course of routine continuation of the tumor in the dba strain, one of the transplants was found to grow with unusual rapidity. Subtransplants of this rapidly growing tumor showed a continuation of this new characteristic. This "new" tumor, called the dBrCX by Strong, was found to grow in all $F_1$'s and $F_2$'s and in all the original dba strain. It also grew in the original nonsusceptible stock, and in other mice irrespective of their genetic relationships. Thus, from a state of high specificity (involving 6 factors), it developed into a tumor completely nonspecific (1 factor), and at the same time showing an increased proliferative vigor. Careful examination in subsequent transplants of the dBrCX revealed another difference in growth between two tumors which thereafter received the terms dBrCm and dBrCsp. The dBrCm gave a 9 : 7 ratio in $F_2$, and the dBrCsp showed a 3 : 1 ratio in the $F_2$.

Strong concluded from the behavior of this tumor that a somatic mutation (the term being used in the broadest sense) can occur within the malignant cell which changes its reaction potential and other physiological activities. He suggested that the nature of the mutational process ". . . may either be a change or shifting of a complete chromosome or chromosomes, or a change or changes within a chromosome or chromosomes (genic), or it may be even cytoplasmic in nature." Such mutational changes as observed by Strong have also been found by Bittner (*32*) and by Cloudman (*33*). The interesting aspect is that in every case the change has been from a condition of high specificity to one of low or no specificity; in other words, from a multiple toward a single-factor condition. As Little (*34*) points out, these sudden changes are properly definable as mutations; however, before

they can be established as "gene" mutations, it will be necessary to find a means for identifying the genes involved. Obviously, if such genes could be identified it would place the somatic mutation theory of cancer on a firm foundation, but the important fact remains that the abrupt changes are self-perpetuating.

In view of the experimental evidence collected in recent years, it may be concluded with some degree of confidence that the somatic mutation theory of cancer does not oppose the facts that have so far been brought to light. Undoubtedly there remains much research to be done before the theory can be either proved or disproved. An analysis of the problem at least makes tenable, for the present, the proposal that the change from the normal to the malignant cell is of the nature of somatic mutation, be it a nuclear or a cytoplasmic change, directly or indirectly involving the division mechanism.

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# *News and Notes*

## Scientists in the News

**Wade Arnold,** executive producer of the National Broadcasting Company, was named as first winner of the American Heart Association's annual Howard W. Blakeslee Award for outstanding scientific reporting on heart and blood vessel diseases. Mr. Arnold was cited for writing and producing "Only One to a Customer," a documentary radio program broadcast last year.

**J. Leroy Bennett,** manager of chemical operations for the Explosives Department of Hercules Powder Company since 1931, has retired after 46 years of service with the company.

**Osborne Bezanson,** chemist, and president of the Chemstrand Corporation, has been named chairman of the board. He will be succeeded as president by **Henry H. Bitler,** now of American Viscose Corporation, the appointments becoming effective Dec. 1.

**M. R. Clarkson,** deputy administrator of the Agricultural Research Administration, has been placed in charge of the Department of Agriculture's program for eradication of vesicular exanthema, a disease of hogs.

President Howard L. Bevis, of the Ohio State University, on April 17 recommended to the University's Board of Trustees that **Byron T. Darling,** associate professor of physics, be dismissed from the University faculty, effective as of that date.

The recommendation was made after a hearing given Professor Darling and attended by the members of the University faculty, the members of the president's office, Professor Darling, Joseph Forer, his counsel, and James C. Harris, assistant professor, Department of Physics.

Dr. Darling's refusal, on the grounds of his rights under the Fifth Amendment, to answer questions put to him by the House Un-American Activities Committee in Washington, March 13, as to whether he then belonged or ever had belonged to the Communist party or any related organization, and whether he had ever performed services for or received funds from that party or such organizations "did grave injury to the University and its faculty," to quote the president. "By refusing to say whether certain of his colleagues were Communists, he cast an unwarranted aspersion upon them individually.

"These considerations lead only to the conclusion that Dr. Darling has shown his unfitness for the position he holds. They show a lack of candor and moral integrity in matters vital to his professorial status. They show gross insubordination to University policy. They show conduct clearly inimical to the best interests of the University."

The University president said that Dr. Darling on the Ohio State campus and throughout the country

". . . is regarded as an outstanding research man and . . . a very good teacher. . . . He appeared consistently during all the time he was on our campus as a competent and devoted man of science. There appeared from his conduct no reason to question his loyalty.

"These facts are relevant and would carry weight," the recommendation continued, "were it not for Dr. Darling's public refusal to answer pertinent questions."

President Bevis' recommendation stated: "The Fifth Amendment is indeed a guaranty that one cannot be required to make statements which can be used as evidence against him in a criminal proceeding. But the Fifth Amendment does not refute the inferences which generally flow from public refusal to answer pertinent questions and does not prevent our consideration of the effect of such inferences in determining the fitness of Dr. Darling to hold professorial rank."

President Bevis quoted from the statement issued March 31 by the Association of American Universities, composed of 37 of the leading institutions of the United States and Canada, of which Ohio State is a member, which said, "There is a line at which 'freedom' or 'privilege' begins to be qualified by 'duty' or 'obligation' . . . . Any member of the University who crosses the duly established line is not excused by the fact that he thinks the line is ill-drawn. . . ."

This statement, which on April 17 was sharply criticized by the Columbia University Chapter of the American Association of University Professors, may be compared with the resolution on "Invoking the Fifth Amendment," adopted by the Annual Meeting of the AAUP in Chicago on March 28. This reads as follows:

"If, in the investigation of members of faculties of institutions of higher education by a Committee of the Congress of the United States or other legislative bodies, a faculty member invokes the Fifth Amendment of the Constitution of the United States as the reason for not replying to questions of the Committee concerning his views and affiliations, and the Committee accepts this reason as a valid constitutional reason for not replying, this the Thirty-ninth Annual Meeting of the American Association of University Professors concurs in the judgment of the Council of the Association, reported to the meeting, that invoking the Fifth Amendment in these circumstances is not, in and of itself, justifiable cause for the dismissal of the faculty member. However, since a decision to invoke the Fifth Amendment involves complex legal and ethical considerations, this statement is not to be construed as advising or generally approving such action by teachers under investigation."

**J. A. Weber,** professor emeritus of anatomy at the University of Geneva, Switzerland, will spend several months in the U. S. as visiting research scientist at Manhattan State Hospital. Dr. Weber will continue his studies on the synapse, with particular emphasis on its structure in brain biopsies of psychotic patients.

## Education

The **Engineer's Council for Professional Development** announces enrollments of 156,080 undergraduates and 20,469 graduate students, fall of 1953, in the 201 institutions in the U. S. and Canada accredited by them.

The **Massachusetts Institute of Technology** will conduct a special Summer Program in Electrical and Optical Methods of Instrumental Chemical Analysis the last two weeks in August. The first program, Aug. 17–21, on electrical methods, will emphasize polarography, potentiometry, conductimetry, amperometric titrations, automatic titration methods, and applications of self-balancing recording potentiometers. The second, on optical methods, Aug. 24–28, will include spectrophotometry (visible and ultraviolet), colorimetry, fluorimetry, turbidimetry, nephelometry, photometric titrations, reflectance techniques, and flame photometry. David N. Hume and Lockhart B. Rogers will be in charge.

The **U. S. Geological Survey** will sponsor a fifth Ground Water School, Aug. 16–29, at the University of Wisconsin for 50 of their young staff geologists and engineers. Candidates for the school are selected by district offices of the Ground Water Branch of the survey. Subjects to be studied will include ground water geology and hydrology, and instruments and methods. There will be at least one field trip, probably to the Baraboo Range-Devil's Lake area.

## Grants and Fellowships

**Allied Chemical & Dye Corporation** announces the award of 38 graduate fellowships for the academic year 1953–1954, to promote study and research in the fields of chemistry and chemical engineering by students in their final year of graduate study. The fellowships will provide $1500 for unmarried fellows and $2000 for married fellows, in addition to payment of tuition, and will be available in 26 universities and other educational institutions in the U. S. and Canada.

The **University of Chicago Medical School,** through the generosity of friends of the late Howard Sloan, has established a $500 annual research grant in the Department of Physiology, to be known as the Dr. Howard Sloan Memorial Research Grant.

The **Muscular Dystrophy Associations of America, Inc.,** have awarded two grants, one of $8343 to the University of Colorado Medical School for work by Heinz Herrmann and his staff; and the other, in the amount of $10,190, to the Worcester Foundation for Experimental Biology, for work by Harris Rosenkrantz and staff.

The **National Science Foundation** has announced approval of 60 grants, totaling $469,550, in the biological and physical sciences, and to support studies and conferences on science and scientific education. This

is the third group of awards to be announced this year for the support of basic research and other matters related to its mission. During the current fiscal year, the foundation has awarded a total of $1,810,200 for 190 grants in support of scientific activities. Since the beginning of the program in 1950, 291 grants have been awarded totaling $2,950,775. The fields included are astronomy, chemistry, developmental biology, earth sciences, engineering, genetic biology, mathematics, molecular biology, physics, psychobiology, regulatory biology, research education in the sciences, scientific information, studies in science, and systematic biology.

The Rockefeller Foundation has made a grant of $30,000 to the **Society of American Foresters** for a study of progress and needs in forestry research in America. The survey will be conducted under the supervision of a committee jointly appointed by the society and the National Research Council. E. L. Demmon, of Asheville, N. C., has been named chairman of the committee. He is vice president of the society as well as the society's representative to NRC's Division of Biology and Agriculture.

## In the Laboratories

The **Agricultural Research Administration** of the USDA announces the following personnel changes in the Division of Weed Investigation: Robert N. Anderson to weed control studies in sugar beets in cooperation with North Dakota Agricultural College, replacing Don E. Kratochvil, who is now at South Dakota State College; Eugene H. Cronin to the halogeton research project at Utah State Agricultural College; Ellis W. Hauser replaces Edward S. Hagood at the Georgia Experiment Station to work on the control of nutgrass and weeds in cotton; Jesse M. Hodgson from Meridian, Idaho, to Montana State College, for aquatic weed and Canada thistle studies; James H. Hughes appointed to the Plant Industry Station staff at Beltsville; Leonard L. Jansen for physiological research on halogeton at Utah State Agricultural College; Melvin K. McCarty will replace D. L. Klingman in June to work on grassland weeds at the University of Nebraska; and Willard C. Robocker will go to the University of Nevada in May to conduct ecological studies on halogeton.

The **Edison Research Laboratory** at West Orange, N. J., has instituted a program combining work as technicians in the laboratory with evening study toward a degree in engineering. It is designed for high school graduates showing aptitude for a science career but whose financial status is such that higher education would be out of the question even with an average scholarship. They are employed full time as laboratory assistants by day, and are enrolled in night classes at the Newark College of Engineering with company financial aid toward their tuition and fees provided they maintain satisfactory records. It is expected that they will obtain their degrees in eight years.

Recent additions to the research staff of the **Miner Laboratories** are: Leonard Laskin, formerly with Monomer Polymer Corporation; Mary Lou O'Connor, formerly with Toni Research Laboratory; and Harris R. Till, Jr., formerly with Western Electric Company.

## Meetings and Elections

The **American Society of Tool Engineers** has elected Roger F. Waindle, of Muskegon, Mich., president, to succeed L. B. Bellamy. Other officers elected at the annual meeting in Detroit were Joseph P. Crosby, Harry B. Osborn, Jr., and Howard C. McMillen, vice presidents; Raymond C. W. Peterson, secretary; and Harold E. Collins, treasurer.

The **Ciba Foundation** will sponsor four symposia during the coming months: "The Peripheral Circulation in Man," O. G. Edholm, chairman, May 11–13; "The Kidney," July 7–9, followed by a general meeting of the Renal Association of the Royal Society of Medicine, July 10; "Humoral and Neurogenic Factors in Hypertension," G. W. Pickering, chairman, July 28–30; and "Experimental Leukemias," Nov. 17–19. Inquiries should be addressed to 41 Portland Place, London, W.1.

A **Sixth Annual Geological Field Conference** will be sponsored by the Department of Geology of Indiana University and the Indiana Geological Survey, May 8–10. Centering attention on "Ordovician Stratigraphy, and the Physiography of a Part of Southeastern Indiana," the party will cross Jefferson, Ohio, and Switzerland counties. Write to Clifty Inn (Headquarters), Clifty Falls State Park, Madison, Ind., for reservations.

The 28th annual convention of the **National Fertilizer Association** will be held at the Greenbrier Hotel, White Sulphur Springs, W. Va., June 15–17. "Efficient Water Utilization" will be discussed by a panel of experts at an open meeting of NFA's Plant Food Research Committee on the morning of June 15. Participants will be W. B. Camp of W. B. Camp & Sons, Bakersfield, Calif.; R. Q. Parks, Division of Soil Management and Irrigation, BPISAE, U. S. Department of Agriculture, Beltsville, Md.; James Ferguson, Memphis, Tenn., who will speak for the Sprinkler Irrigation Association, Washington, D. C.; and H. H. Tucker director, Coke Oven Ammonia Research Bureau, Columbus, Ohio, and chairman of the committee, who will preside. Addressing the first general session, June 16, will be Hugh M. Comer, president, Avondale Mills, Sylacauga, Ala.; the Honorable True D. Morse, Under Secretary of Agriculture, Washington, D. C.; and Louis Ware, president, International Minerals & Chemical Corporation, Chicago, who will speak in his capacity as chairman of the Association's Board of Directors. At the second general session, June 17,

Russell Coleman, NFA's president will lead off in a panel discussing "Proper Use of More Fertilizer," with Roy Battles, Assistant to the Master, The National Grange, as moderator. The following will take part: Milton C. Cummings, president, Farmers and Merchants State Bank, Effingham, Kans., representing the credit agencies; Werner L. Nelson, in charge, Soil Fertility Research, School of Agriculture, North Carolina State College, representing the Land Grant Colleges; Frank W. Parker, Director of Soils Research, BPISAE, U. S. Department of Agriculture; and W. F. Price, Plant Food Division, Swift & Company, Chicago, speaking for the fertilizer industry.

The **Rutgers University College of Pharmacy** will sponsor the University's Second Annual Pharmaceutical Conference, May 13, for the discussion of problems of the pharmaceutical and allied health professions. Speakers include: Walter E. Hoadley, Jr., of Armstrong Cork Co., Lancaster, Pa., on the economic outlook; Floyd E. Blauch, of the Federal Security Agency, on pharmaceutical education; Seymour Jeffries, of Brooklyn College of Pharmacy, on drug store merchandising; and William Pleuthner, of Batten, Barton, Durstine & Osborne, on public relations. The afternoon session will feature a panel discussion with Robert P. Fischelis, secretary of the American Pharmaceutical Association, as moderator.

The **Springfield (Mass.) Chapter, AAAS,** will meet on April 30 in the Springfield Museum of Natural History. James L. Tullis, associate director of the Blood Characterization and Preservation Laboratory at Harvard, will talk on "Research Developments in the Collection, Separation, Preservation, and Uses of Blood."

## Miscellaneous

The Submarine Thermal Reactor prototype plant has successfully entered its first phase of operation at the **U. S. Atomic Energy Commission** National Reactor Testing Station in Idaho. This phase is known as "criticality" and means that the nuclear components of the reactor are sustaining an atom fissioning chain reaction. Further testing and operation will continue, and the plant will be brought to full power gradually in order to determine the operating characteristics of the similar plant which will power the USS "Nautilus," and to train the crew for this vessel. It is expected that such operation will add to the significant contributions to reactor technology already made through experimentation, design, and construction of the STR. The STR plant in Idaho and the similar plant for the "Nautilus" have been a joint project of the AEC's Argonne National Laboratory, the Atomic Power Division of the Westinghouse Electric Corporation, and the Electric Boat Division of the General Dynamics Corporation, assisted by numerous subcontractors.

A resolution (H. J. Res. 166) for establishing a **Joint Committee on Science** has been introduced in Congress by Representative Carl Hinshaw (R., Cal.). The committee would consist of seven members from each house, together with "such other members as shall signify their intention" of joining. The purpose of the proposed committee, as defined in section 2 of the resolution, follows: "In order to promote a better understanding of the actual and potential impact of science upon public affairs, including human and natural resources, interstate and foreign commerce, relations with foreign nations, the common defense and security, and the national health, prosperity, and welfare, the committee shall endeavor to keep itself informed with respect to, and bring to the notice of Members of Congress, the results of scientific research and technical development which bear upon public affairs, and the problems being encountered in maintaining in the U. S. a scientific and technical effort of outstanding quality and accomplishment." The committee would work closely with the National Science Foundation and other agencies.

The **National Citizens Committee for Educational Television,** Ring Building, Washington 6, D. C., has issued a pamphlet, "Educational Television—An Opportunity Equal to Invention of Printing," which will prove both informative and helpful to those concerned with the framing of applications for the 242 channels reserved by the FCC for educational purposes. Copies will be supplied without charge.

The **National Geographic Society** and the **Marine Laboratory of the University of Miami** at Coral Gables are conducting a long-range investigation into the lives of the pelagic fishes, including the tarpon and sailfish of sportsmen and the food fishes such as tuna and mackerel which can fortify with protein the diets of millions of people. This work is a continuation and enlargement of the intensive study of the oceanic plankton which the National Geographic Society and the Marine Laboratory have pursued over the last two years. F. G. Walton Smith, head of the Marine Laboratory since 1940, has been named director of the pelagic fishes investigation. He will be assisted by Hilary B. Moore, oceanographer, and by some 60 scientists and graduate students of the laboratory.

The **National Science Fair,** sponsored by leading newspapers and Science Service through its Science Clubs of America, will be held at Oak Ridge, Tenn., May 7–9. About 70 high school students, winners in local fairs, will exhibit their scientific achievements. Awards will be presented in various categories. The judges include: from the Oak Ridge Laboratory and Atomic Energy Commission, G. A. Andrews, R. A. Charpie, L. B. Emlet, Alexander Hollaender, C. E. Larson, R. S. Poor, Elizabeth Rona, H. N. Roth, Morse Salisbury, C. S. Shoup, A. H. Snell, J. A. Swartout, and A. M. Weinberg; and C. L. Comar from the University of Tennessee and Carl Seyfert of Vanderbilt University.

# *Technical Papers*

## Reversal of Gram-staining Behavior

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In a recent article, Bartholomew and Mittwer (*1*) report the conversion of gram-positive organisms to gram-negative ones by ultraviolet irradiation. In two recent papers (*2, 3*) we proposed a mechanism for the gram-staining reversal and showed that gram-positive bacteria, as well as alkali-treated wool, could be converted to a gram-negative state by acids or by oxidizing agents and could be reversed back to the gram-positive state by means of alkalis or by reducing agents.

Bartholomew and Mittwer's results appear at first sight to be contrary to the view expressed in our discussion of the possible role of ultraviolet light on the gram-staining reversal (*2*). On further study, however, the results of Bartholomew and Mittwer actually bring added evidence for the mechanism postulated. Meunier (*4*) has shown that the action of light on wool is to make the sulfur more labile and to convert the cystine sulfur to sulfur dioxide and finally to the trioxide, which is freed in the form of sulfuric acid. The experiments of Smith and Harris (*5*) also indicate the formation of sulfate by the photochemical oxidation of wool. Moreover, this was shown to be accelerated by the presence of acids. The formation of hydrogen sulfide appears to be the first step in this process. The protective action of formaldehyde on the degradation of proteins, and of wool in particular, is well known.

It thus seems that the action of reducing agents and of oxidizing agents in the gram-staining mechanism which we postulated can also explain the results of Bartholomew and Mittwer. The action of ultraviolet radiation is probably the following. The first step is a reducing or hydrolytic one whereby —SH and —SOH groups are formed from the cystine linkages. This was the reason for supposing that gram-negative organisms would be converted to gram-positive ones. Mirsky and Anson (*6*) found also that ultraviolet light liberates —SH groups in many proteins. This first step might explain why the formation of gram-negative cells observed by Bartholomew and Mittwer was slow at first and seemed to require an induction period. However, the initial formation of —SH groups is superseded by an oxidation which results in gram-negative response, as we have already postulated. Since formaldehyde has a protective action and a reducing one, its retarding effect on the conversion noted by Bartholomew and Mittwer is readily understood. On the other hand, osmic acid, being oxidizing, would hasten the reaction as observed by Bartholomew and Mittwer. The accelerating effect of acids noted by Smith and Harris (*5*) should be recalled in this connection.

Thus the changes in gram-staining behavior mentioned above emphasize once more the analogy between the behavior of the cytoplasmic membrane of gram-negative bacteria and that of untreated wool, as well as that between gram-positive bacteria and alkali-treated wool (*2*). The role of the ribonucleic acid in the gram stain reversal was also discussed in the above-cited communication.

[1] Present address: Laboratory for Psychiatric Research, Regina General Hospital, Regina, Sask., Canada.

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Manuscript received August 25, 1952.

## Formation of a Labile Pigment in Rabbit Ova During Histochemical Demonstration of Succinic Dehydrogenase[1]

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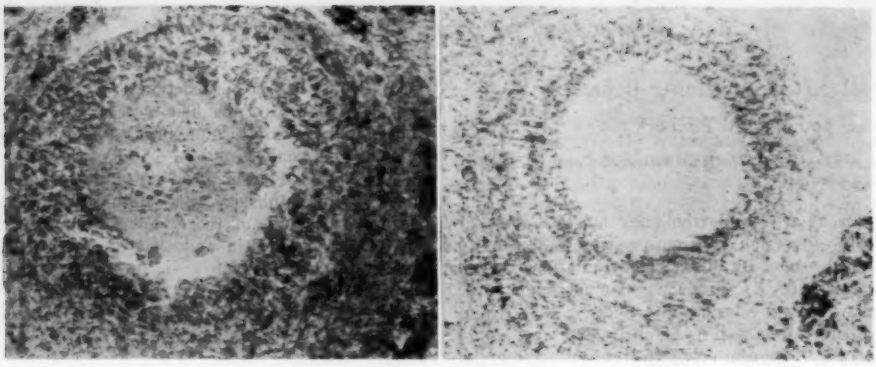
The histochemical demonstration of succinic dehydrogenase, one of the vital respiratory enzymes, has been previously described (*1–3*). The reaction is based on the reduction of a tetrazolium salt during incubation of fresh tissue in the presence of an excess of sodium succinate (*1*). If neotetrazolium (*pp'*-diphenylene bis 2-(3,5 diphenyl tetrazolium chloride)) (NT) is employed, the reduction of NT is not reversible (*4*). The reduction compound is seen as fine black granules in the cells.

Previously, we demonstrated succinic dehydrogenase activity in ovaries of rabbits injected with urine from pregnant or nonpregnant women (*3*). Fresh 3-mm blocks were incubated for 1 hr at 37° C in 0.9% NT in normal saline with 0.1 *M* phosphate, buffered to pH 7.4 with the addition of 0.03 *M* sodium succinate. The blocks were fixed in formalin neutralized with magnesium carbonate. Twenty-four hr later, frozen sections (15 μ) were cut from the blocks. In the 18 rabbits reported in this series (*3*), as well as in 4 other rabbits separately studied, little or no black pigment

[1] This investigation was supported by a research grant C-1486 from the National Cancer Institute, of the National Institutes of Health, USPHS.



A B

FIG. 1. Frozen section (15 μ) of rabbit ovary incubated in NT with succinate. Succinic dehydrogenase demonstrated by deposition of pigment. ×600. *A*, section prepared 24 hr after incubation, with granular black pigment in follicle cells, light staining of zona pellucida, and microdroplets in ovum. *B*, section from same block after 4 weeks' storage in formalin. Little change in distribution pattern of granular black pigment. Ovum and zona pellucida are now colorless.

was seen in the ova, whereas the adjacent follicle cells contained appreciable quantities of black granules. In addition, a reddish pigment was found in varying quantities through the ovaries, interspersed with the black pigment granules. Only in the ova, however, was this reddish pigment found alone. Here it was seen as microdroplets of varying size, rather than the granule or crystal formation suggested by the black reduced NT in other portions of the ovaries. When additional sections were cut from the same ovaries 4 weeks later (in part as a control procedure) all reddish pigment, including that from the ova, had disappeared. The black pigment of reduced NT seemed unchanged in amount and distribution.

As a further investigation, additional blocks of ovaries of 3 rabbits receiving no urine injections were similarly processed in NT with succinate. All blocks were fixed in formalin neutralized with magnesium carbonate having a pH of 9.2. In the frozen sections cut 24 hr later, black granules, some resembling short needlelike crystals (*2*), were found in follicle cells, in cystic follicles, and in the stromal cells, as previously described (*3*). Virtually no black granules were found in the ova. A less prominent reddish pigment deposition was mingled with the black granule deposits. The reddish droplets were also found in moderate quantity in the ova (Fig. 1 *A*) with light pink staining of the zona pellucida. After 4 weeks, the mean pH of the fixative had declined to 7.7. Additional frozen sections from the blocks at this time showed complete disappearance of all reddish pigment, including that seen in the ova (Fig. 1 *B*). The ova were colorless. The black pigment granules retained the previous pattern.

It is possible that a certain element of this reddish staining may represent dissolved reduced NT in the abundant lipoidal content of the ovary. This type of staining of fat during dehydrogenase demonstration has been reported by Seligman and Rutenburg (*1*). We have observed such lipoidal staining in hilar fat attached to ovaries being incubated in NT with succinate. This staining also disappeared on storage in formalin. It is our impression, however, that, at least in part, the formation of reddish pigment in the ova in the current study is an incomplete reduction compound of NT, based on the following:

1. In an analogous situation, Seligman and Rutenburg reported formation of a reddish-purple color in areas where enzymatic activity was low, by partial reduction of a tetrazolium salt to a monoformazan. They suggested that the reduction potential may have been lower than in areas stained blue (*1*).

2. The reddish staining of hilar adipose tissue attached to ovaries being processed in NT with succinate resulted in a diffuse reddish coloration, rather than the microdroplet formation found in the present study.

3. After formalin fixation, the ovaries from 7 rabbits, as well as human and rabbit adipose tissue in the current study, did not respond in any manner to incubation in NT with succinate (*1*).

4. In our experience, use of this technique with preparation of frozen sections 24 hr after initial processing in NT has resulted in admixture of small amounts of reddish-brown pigment with the blue-black formazan in various areas of 100 cervical biopsies, including regions not commonly considered to contain stainable lipoid (*5*).

The evanescence of the reddish pigment suggests the formation of a different chemical compound in this phase of the reaction. It does not seem related to disappearance of fat, since after the 4 weeks' storage, frozen sections from the ovaries in the current series showed abundant reaction in the ova to a conventional fat stain such as scarlet red. Reduced NT, in the form of blue-black pigment formation, showed little change in pattern with the passage of time, in our studies. The reduction of NT to the purple to black compound was not considered reversible by Antopol and co-workers (*4*).

It is reasonable to assume that the presence of the

labile reddish pigment within the rabbit ova as the sole manifestation of succinic dehydrogenase may signify the presence of a localized lesser degree of activity of this enzyme than found in certain other components of the ovary.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Manuscript received September 11, 1952.


## Paper Chromatography of Corticosteroids


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The paper chromatography of corticosteroids has been reported by other workers (*1–3*) and has generally given rise to reliable methods for the identification of such of these steroids as are known compounds. The present communication relates to a procedure for the paper chromatography of corticosteroids, in which a number of the usual techniques employed are simpler and more rapid than those previously described.

Although the present procedure is applicable to both descending and ascending paper chromatography, it has been more frequently applied to the latter and will be described as such. A sheet of Whatman No. 1 filter paper (43 × 43 cm) is folded into a cylinder in the manner indicated by Wolfson *et al.* (*4*). The materials to be chromatographed are applied to the paper as droplets of the appropriate solutions at points about 2 cm apart on the starting line, the latter being 8 cm from the bottom fold of the paper, and the spots formed by the droplets being not greater than about 0.5 cm in diameter. The paper is then placed in a cylindrical glass jar 15 cm in diameter and 46 cm high (Fisher Scientific Co., New York) containing a one-phase solvent mixture of xylene (225 ml) and absolute methanol (75 ml), and the jar is subsequently closed by means of a gastight cover. The solvent is allowed to ascend on the paper to a distance of about 25 cm from the starting line—this occurs over a period of about 2.5 hr. The paper is then removed from the jar and air-dried. Visualization of the locations of the various steroids and their quantitative estimation may then be performed by any of the known procedures (*1–3, 5–8*).

The $R_f$ values obtained with a number of authentic corticosteroids[1] are shown in Table 1. It will be observed that drying the paper prior to chromatography results in a change of the $R_f$ values. In general the results obtained with predried paper were found to be more reproducible, predrying presumably minimizing partition phenomena involving the moisture that may otherwise be present on the paper.

Whenever the quantities of materials applied to the starting line on the paper are equivalent to about 5 μg of standard corticosteroid, there is obtained, after development and visualization of the location of substances, a number of discrete spots corresponding to the various steroids present. Approximate dimensions of the various spots obtained are included in Table 1.

Advantages of the above procedure over those reported in the literature are as follows: A one-phase solvent system is used throughout, rendering unnecessary the equilibration of the paper in the solvent vapors prior to development; pretreatment of the paper with any solvent is unnecessary; lateral diffusion of steroid spots during development is quite limited, thus rendering unnecessary the precutting of the paper into a pattern of separated strips; the development period required for the resolution of mixtures of corticosteroids is not greater than 2–3 hr; air-drying of the paper afterwards is completed in less than 30 min.

TABLE 1

| Corticosteroid | | Paper dried 15 min at 100° C prior to development | | Paper not dried prior to development | |
|---|---|---|---|---|---|
| Chemical Name | Letter Designation | $R_f$ | Spot dimensions (horizontal × vertical diameter) cm | $R_f$ | Spot dimensions (horizontal × vertical diameter) cm |
| 11-Desoxycorticosterone | Q (Reichstein) | 0.921 | 0.9 × 1.0 | 0.826 | 0.8 × 1.7 |
| 11-Desoxy-17α-hydroxycorticosterone | S " | .698 | .7 × 5.5 | .495 | .9 × 3.8 |
| Corticosterone | B (Kendall) | .653 | .6 × 4.7 | .491 | .9 × 2.9 |
| 11-Dehydro-17α-hydroxycorticosterone | E " | .501 | .8 × 3.5 | .394 | 0.7 × 0.9 |
| 17α-Hydroxycorticosterone | F " | 0.362 | 0.7 × 3.5 | 0.312 | 1.1 × 1.3 |

As in the case of the previously reported procedures for the paper chromatography of corticosteroids, the $R_f$ values obtained by the present procedure are relative rather than absolute. Further, it is considered essential to base the final identification of an unknown corticosteroid on a direct comparison with authentic specimens of known substances, employing such criteria as specific color reactions (*6, 7*) and absorption spectra of sulfuric acid chromogens (*8*).

[1] Samples of corticosterone and 17α-hydroxycorticosterone were generously donated by Carl Djerassi and Gregory Pincus, and were kindly obtained for us by B. J. Brent.

The above-described procedure has also been successfully employed on a smaller scale using, most frequently, a 500-ml measuring cylinder of conventional type as the chromatographic vessel. Such a system was found to provide a convenient means of performing quick checks on the identity and state of purity of corticosteroids and related substances.


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Manuscript received September 2, 1952.


## Microanatomical Study of DDT-moribund *Anopheles quadrimaculatus* Say


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Histological studies following administration of DDT have been made principally on the roach (*Periplaneta americana* L. [*1, 2*]), on the honeybee (*Apis mellifera* L.[*1*]), and on the housefly (*Musca domestica* L. [*3*]). For the most part these studies were made on one stage only and did not include examinations of all the tissues of these insects.

Since the action of DDT still remains obscure, it seemed advisable to make intensive histological studies of *all* the tissues of an insect from representative periods during its life span. The common malaria mosquito of the Southeastern United States, *Anopheles quadrimaculatus* Say, was selected for these studies.

Fourth-instar larvae, pupae, and adults of both sexes were exposed topically to massive doses of pure *p,p'*-DDT, and when moribund (about 2–8 hr) were studied by examination of dissected living specimens and by examination of sectioned fixed specimens. All test animals were acutely poisoned and showed every sign of extreme intoxication. Twenty-five test animals from each stadium were used with equivalent numbers of controls.

Dissections were made in insect Ringer's and were either examined while fresh under the microscope with and without phase contrast, or were examined after fixation with alcohol or formalin in whole mounts prepared of the various tissues.

Complete transverse, sagittal, and frontal serial sections at 6–15 μ were made from alcoholic–formalin-, Bouin-, or Carnoy-fixed material. Sections stained with Delafield's and Haidenhain's iron hematoxylin and counterstained with eosin were examined at 100 and at 1000 diameters.[1]

Every effort was made to study all the representative tissues of these insects and to determine by comparison with controls whether visible changes in the structure and staining reactions had occurred. Detailed cytological, histological, and histochemical studies of normal *A. quadrimaculatus* are in preparation for publication at a later date.

Tissues examined included: (1) hypodermis; (2) tracheae; (3) thoracic molting glands in larvae; (4) micro- and macro-oenocytes; (5) imaginal discs of undifferentiated and differentiated thoracic and abdominal muscles; (6) imaginal discs of eyes, antennae, legs, wings, and halteres; (7) anal papillae of larvae; (8) neurocytes and neuropile of frontal, supraesophageal, thoracic, and abdominal ganglia; (9) neurosecretory cells in supraesophageal ganglion; (10) corpora allata–cardiaca complex; (11) immature, differentiating, and mature gonads and associated structures (mucus gland, atrium, spermatheca of female and accessory glands of male); (12) dorsal vessel; (13) alary muscles; (14) micro- and macro-pericardial cells; (15) thoracic ventral nephrocytes in larvae; (16) ventral diaphragm of adult; (17) internal and external fat body; (18) buccal cavity; (19) salivary glands; (20) esophagus; (21) gastric caecae of larvae; (22) dorsal and ventral diverticula of adult (23) midgut; (24) Malpighian tubules; (25) hind-gut; and (26) rectal papillae of adult.

No microanatomical changes in cell or nuclear structure (e.g., cytoplasmic vacuoles, hypertrophy, atrophy, surface irregularities, karyorrhexis) or abnormal reactions to hematoxylin and eosin (e.g., overstaining, diffuse staining, blotching, or failure to stain) were encountered in any of the tissues of any of the stages that were examined. These findings indicate that DDT does not operate to produce visible structural damage to cells during representative periods of the life span of *A. quadrimaculatus*.

The present observations confirm and extend those of Richards and Cutkomp (*2*), who found absence of definite pathology in DDT-poisoned roaches. No comparison can be made between the present observations and those of Chang (*1*), who reported breakdown of Golgi bodies in the ganglia of DDT-poisoned roaches and honeybees, since the special methods required for their demonstration were not used in the present studies.

Absence of definite pathology in the central nervous system of the mosquito and the roach following DDT administration is not peculiar to insects, for similar findings have been reported by Globus (*4*) in monkeys, dogs, cats, and rats acutely poisoned with DDT.

A few investigators have reported cellular changes in insects (*1, 3*) and in vertebrates following DDT


[1] Grateful acknowledgment is made to Ralph D. Lillie and James H. Peers, Laboratory of Pathology and Pharmacology, for extending me the courtesy of their laboratory facilities. I am indebted to Joseph Woodard of their laboratory for having cut and stained most of the sections.

administered in different ways, but these changes are generally considered to be nonspecific (*2, 4*) and do not adequately account either for the symptoms or for the death of the animals (*2, 4, 5*).


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Manuscript received August 19, 1952.


## A Rapid Screening Test for the Determination of the Approximate Cholinesterase Activity of Human Blood


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Organic phosphate insecticides are coming into extensive use. The chief physiological action of these highly toxic compounds is their inhibition of the cholinesterase (ChE) activity in man, as well as in insects. Compounds having a similar action are considered as possible war gases. Among the first symptoms to appear as a result of overexposure to these compounds are nausea, vomiting, diarrhea, and headache. In very severe poisoning weakness and generalized muscular fasciculations also appear. Since these symptoms are nonspecific, it is important to know whether or not they are caused by ChE-inhibiting agents. The most practical method of detecting the true cause of the symptoms is the determination of the ChE level of the blood, which reflects the activity of the enzyme in all parts of the body.

The methods commonly used to determine blood ChE activity require apparatus found only in clinical or chemical laboratories. For screening purposes a simpler and more generally applicable test is desired, by which overexposure may be detected so that appropriate treatment could be administered with minimum delay.

Although plasma ChE is inhibited more readily than red cell ChE (*1–3*), in cases of actual human poisoning by organic phosphate insecticides both plasma and red cell ChE levels were significantly reduced (*2–4*). It seemed, therefore, that the whole-blood ChE level would serve equally well as an index of overexposure. Based on this premise, a rapid screening test that can be carried out in the field without the use of specialized equipment has been developed and is the subject of this report.

This method is essentially a visual colorimetric method in which the change in pH (ΔpH) resulting from the liberation of acetic acid from a ChE substrate (acetylcholine iodide) is estimated by the change in color of an indicator, brom thymol blue (BTB). The color of the solution at the end of 20 min will determine the approximate ChE activity. Only one drop of fingertip blood is required.

The only apparatus and materials required are a blood-diluting pipette (WBC dilution, 1:20), a dropping pipette with bulb attached, a 2- and a 1-ml rubber-stoppered serum bottle containing acetylcholine iodide[1] (6 mg) and brom thymol blue[2] (0.5 mg), respectively, and two 1-ml bottles each containing 1 ml of sterile distilled water (pH 6.8–7.0). The reagents can be added to the bottles by dissolving them separately in alcohol (300 mg substrate/25 ml and 25 mg indicator/10 ml) and adding 0.5 ml of the substrate solution to the 2-ml bottle and 0.2 ml of the indicator solution to the 1-ml bottle. After stoppering the bottles, the alcohol is removed under reduced pressure at room temperature by inserting a hypodermic needle through the rubber stopper. Before using, 1 ml of distilled water is added to each of the reagent bottles by means of the dropping pipette, and the bottles are shaken. One of the bottles that had contained distilled water can then be used as the test bottle. Acetylcholine iodide was used as the substrate because it is nonhygroscopic and stable (*5*). All these materials are easily incorporated into a small kit that can be carried in the pocket.

Because this method is based on a change in pH, the finger from which the blood sample is to be taken, as well as the lancet, must be uncontaminated with acid or alkali. After being washed with water and sterilized with alcohol, both the fingertip and the lancet must be wiped dry. After pricking the finger, blood is drawn up to the 0.5 mark on the pipette, and then the outside of the pipette is wiped with a clean piece of gauze. The blood sample is diluted with BTB solution up to the 11 mark. The blood-BTB solution is then expelled into the empty bottle, and any remaining blood in the pipette is washed into the bottle by drawing the blood-BTB solution up and down several times. A second volume of BTB is drawn up to the 11 mark and added to the blood-BTB in the test bottle. Two volumes of the substrate solution, each measured to the 11 mark, are then added to the blood-BTB solution. The test bottle is stoppered and shaken. After noting the color of the solution (it should be green) and the time, the test bottle is immediately placed in the axilla next to the skin so that the test will be carried out at constant (body) temperature. At the end of exactly 20 min the color of the solution is again observed, preferably in daylight or fluorescent light, by holding a piece of white paper about 1 in. below the bottle held in a horizontal position and looking *down* through the side of the bottle.

[1] Hoffmann-La Roche.
[2] Harleco, water-soluble.

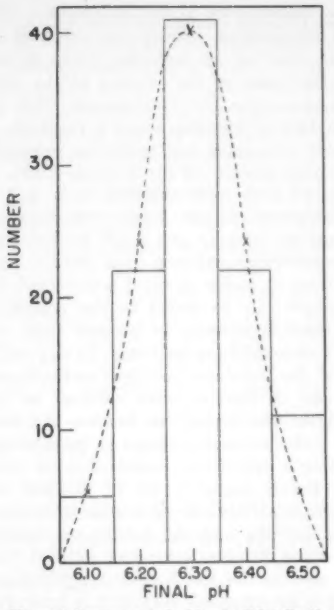


FIG. 1. Normal human whole blood: Distribution of final pH values in cholinesterase activity determinations on 101 subjects (52 white males and 49 white females, ages 19–62). ———— = histogram of determinations; – – – – – = calculated normal curve.

With this method, approximate whole-blood ChE activities of 52 white males and 49 white females between the ages of 19 and 62 were determined. The results were checked by the glass electrode. In the case of 92% of the people tested by the color indicator method, the test solution had an orange color at the end of 20 min. The remainder of the test solutions had an orange-brown color.

The initial pH of the whole-blood test solutions was found to average 7.22, with a range of 7.20–7.35 when determined by the glass electrode within a few minutes after the blood samples were taken. However, because of the loss of carbon dioxide from the blood, higher pH readings are obtained when the solutions are exposed to the atmosphere for any length of time. For this reason the final pH of the test solutions was considered to be the only criterion of ChE activity. In Fig. 1 it can be seen that the final pH range of the samples varied from 6.05 to 6.55, with a mean of 6.30 and standard deviation of 0.10. A final pH of 6.30 or less was considered to represent 100% activity, and pH 7.22 represented zero activity. On this basis a final pH of 6.50 (two standard deviations from the mean) is equal to an activity of 78%. Thus 96% of the individuals tested had a whole-blood ChE activity of 78–100%. The individuals whose color test solutions were orange-brown were also found to have low whole-blood ChE activities, based on the final pH of their test solutions.

The color of the test solutions at the end of 20 min was correlated with the final pH by using the glass electrode. A range of ChE activities (0–100%) was achieved by inhibiting the ChE to various degrees by the addition of varying amounts of sodium fluoride. The following color scale for ChE activity was thus devised: orange, 100%; brown, 75%; olive-brown, 50%; olive-green, 25%; and green 0%.

In addition to determining the whole-blood ChE activities of the individuals tested, ChE activities of plasma and red cells were also determined, using Michel's method (*6*). Individuals found to have orange-brown test solutions and low whole-blood ChE activities were also found to have either low plasma or both low plasma and low red cell activities.

No statistically significant differences were found between the whole-blood, plasma, and red cell ChE activities of the four age groups tested, or between men and women. However, it can be seen from Table 1 that in each age group the men had a slightly higher plasma activity than the women. The mean ΔpH value of 0.76 obtained for the activity of red cells from both males and females agree very closely

TABLE 1

| | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Age Group | 19–29 | 30–39 | 40–49 | 50–60 | Total | 19–29 | 30–39 | 40–49 | 50–62 | Total |
| Number | 16 | 11 | 10 | 15 | 52 | 15 | 9 | 10 | 15 | 49 |
| Whole Blood | | | | | | | | | | |
| Mean final pH* | 6.25 | 6.39 | 6.31 | 6.28 | 6.29 | 6.31 | 6.28 | 6.31 | 6.37 | 6.32 |
| SD | 0.12 | 0.08 | 0.12 | 0.09 | 0.107 | 0.084 | 0.075 | 0.098 | 0.102 | 0.093 |
| Mean percentage Activity* | 98 | 93 | 96 | 99 | 96.8 | 98 | 99 | 96 | 94 | 96.6 |
| SD | 6.0 | 7.0 | 6.4 | 2.2 | 5.7 | 4.3 | 2.3 | 5.7 | 8.3 | 6.0 |
| Plasma | | | | | | | | | | |
| Mean ΔpH* | 0.92 | 0.99 | 0.86 | 0.88 | 0.91 | 0.75 | 0 86 | 0.66 | 0.79 | 0.76 |
| SD | 0.17 | 0.15 | 0.20 | 0.17 | 0.16 | 0.16 | 0.27 | 0.17 | 0.16 | 0.18 |
| Red Cells | | | | | | | | | | |
| Mean ΔpH* | 0.70 | 0.77 | 0.78 | 0.81 | 0.76 | 0.74 | 0.74 | 0.78 | 0.74 | 0.76 |
| SD | 0.09 | 0.08 | 0.08 | 0.09 | 0.03 | 0.10 | 0.09 | 0.14 | 0.09 | 0.03 |

* Differences between age groups and between men and women are not statistically significant.

with the value of 0.753 obtained by Michel for males (*6*) and the values obtained by other investigators for both males and females, but is lower than the value of 0.861 obtained by Wolfsie and Winter (*7*). The value obtained for plasma activity of males (0.91) was higher than the value found by Michel (0.703) but agrees with the value obtained by Wolfsie and Winter (0.912).

The symptoms caused by overexposure to anti-ChE agents usually do not appear until the ChE level of the plasma is near zero and that of the red cells is below 30% (*2, 3*). Since the color indicator method can detect 75% or less of normal activity, it should be quite adequate for relating symptoms to ChE activity. If the symptoms are found to be due to a low ChE activity, atropine should be administered immediately in recommended doses (*8, 9*).

In addition to relating symptoms to ChE activity, the color indicator test could be used as a screening test to detect individuals having a low ChE activity either as the result of overexposure to anti-ChE compounds or as the result of some pathological condition. A ChE activity below 75% should dictate the removal of such an individual from further exposure to anti-ChE compounds until his ChE activity returns to normal.

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Manuscript received August 19, 1952.

## Mutation of Mating Type in *Saccharomyces cerevisiae*[1]


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Two mating type genes (*a* and α) were first described in *Saccharomyces cerevisiae* by Lindegren and Lindegren (*1*). These authors reported that haploid cultures maintained vegetatively may ultimately lose their mating ability, but noted no interconversion between *a* and α. Leupold (*2*) has found that mating type in the yeast *Schizosaccharomyces pombe* is mutable, apparently in all directions. Such mutability has not been proved in *S. cerevisiae*, although it has been inferred by Winge (*3*), based on the observation that

[1] Work performed under Contract No. W-7405-eng-26 for the Atomic Energy Commission.

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TABLE 1

Segregation of Ascospores from a Cross Between A176.1 (*a* Tr⁻ Me⁻ Ad+ Ur+) × A191.1 (*a* Tr+ Me+ Ad⁻ Ur⁻)*

| Ascospore | M.T. | Tr | Me | Ad | Ur |
|---|---|---|---|---|---|
| A667.1 | α | + | + | + | − |
| A667.2 | α | + | − | + | + |
| A667.3 | a | − | − | − | + |
| A667.4 | a | − | + | + | − |
| A668.1 | a | + | − | + | − |
| A668.2 | a | − | − | − | + |
| A668.3 | α | − | + | + | − |
| A668.4 | Died | | | | |
| A670.1 | α | + | − | + | + |
| A670.2 | a | − | + | + | − |
| A670.3 | a | − | − | − | − |
| A670.4 | Lost during dissection | | | | |
| A671.1 | a | − | + | + | + |
| A671.2 | α | + | − | − | − |
| A671.3 | a | − | − | + | + |
| A671.4 | Died | | | | |

* Tr = tryptophan-synthesizing gene; Tr+ = independent of tryptophan requirement; Tr⁻ = requires tryptophan for growth; Me = methionine; Ad = adenine; Ur = uracil; M.T. = mating type.

"a diploid area . . . is frequently encountered at the margin of an otherwise haploid colony. . . ."

To examine this question directly the following experiment was carried out. A haploid clone of *a* mating type, which required tryptophan and methionine for growth, was mixed with another *a* haploid which required adenine and uracil. The cells were handled as described elsewhere (*4*) for prototroph recovery. Controls were run with each haploid alone. One ml of each washed cell suspension was plated on minimal agar (lacking tryptophan, methionine, adenine, and uracil). Neither control plate had any colonies; i.e., the frequency of double mutation was too low to be revealed by the plating method. The plate in which the mixture had been plated had about 10 colonies. Several of these were isolated and induced to sporulate.

The segregation data for one of these isolates are shown in Table 1. Mutation of mating type from *a* to α has probably occurred to give rise to the observed results. Ascus A667 segregates 2*a* : 2α, and the three incomplete asci show heterozygosity for mating type. It may be noted that A667 yields a 3+ : 1− ratio for the adenine gene. Population analyses run on the independent cultures revealed no heterogeneity, suggesting that mutation occurred very early in ascospore development or germination. It is unlikely that there is a significant correlation between the mutation for mating type (which must have occurred prior to conjugation) and that for adenine independence (which must have occurred after fusion).

These data, demonstrating mutation of mating type prior to a cross between two *a* haploids, do not rule out the possible occurrence of an *a* × *a* cross, giving rise to an "illegitimate" diploid (*5*). Such diploids would be homozygous for mating type, and have been reported to sporulate only poorly if at all. It has been

our experience that diploids homozygous for mating type, arising from the segregation of triploids and tetraploids (*6*), fail to sporulate and would correspond quite well to this feature of the "illegitimate" diploid. Thus, part of the difference between the views of Winge and Roberts (*7*) and Lindegren (*5*) on "legitimate" and "illegitimate" diploids may be due to studies of fundamentally different material—namely, diploids that had arisen from mutation of mating type as opposed to diploids that had arisen through a mating of haploids of like mating type.

The present data provide direct evidence that mutation of mating type occurs.[3] With our material, the frequency of such spontaneous mutation appears to be too low to affect significantly segregation data.


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Manuscript received September 2, 1952.


## A Naturally Occurring Antiauxin[1]


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Three crystalline substances have been separated from the extract obtained from flowering plants some five years ago (*1*). Two of these were isolated by high vacuum distillation at 125° C and fractional crystallization using ether and chloroform as solvents.[2] A third substance has been recovered from the distillation residue, with warm chloroform. This crystalline fraction has been found to have the characteristic of inhibiting callus formation induced by naturally occurring or applied auxin on wound surfaces. This callus-inhibiting property is demonstrated by placing ¼–½ mg of crystals of the substances in a longitudinal slit made in the third and fourth internodes from the tips of cocklebur plants (*Xanthium* sp. in Wisconsin). Callusing is encouraged by binding the slit stems with moist sphagnum moss. Callus tissue does not form when the crystalline material is present. Extracts from alfalfa, avocado, barley, cocklebur, and Sudan grass have given callus-inhibiting results similar to that of the crystalline material from oats used in the tests reported here.

A second test of the antiauxin property of the crystalline material was made by measuring its effect upon inhibiting epinasty induced by indolacetic acid. A test is made as follows: 0.8–0.9 mg of the crystals (originally extracted from oats in the boot stage) were placed in logitudinal slits in the sixth internode from the base of 12 weeks' old cocklebur plants. Control plants without crystals were also slit. Three to 10 days after the time of applying crystals various lots of plants were sprayed with several concentrations of indolacetic acid. Plants that had been previously implanted with crystals developed less epinasty (Fig. 1). The amount of epinasty was determined by measuring the angle between the stem axis and a line extending from along the petiole where it attaches to the leaf blade and subtracting from this value the averaged angles of leaves of the same ages on untreated plants. The mature leaves at the fifth to eighth nodes from the tip of the stem were used in determining the degrees of epinasty. The averaged results of four experiments are shown in Fig. 2. Two to 4 plants for each concentration of indolacetic acid were used in each experiment.

The reason for using dry crystals in the slit plants instead of a solution that would give a more quantitative measurement is that the crystalline substance is not soluble in solvents that are practicable for use with plants. It was determined that cocklebur plants become "saturated" at a low level of active extract: triple dosages of crystals applied by using 3 slits/plant gave no more inhibition of auxin activity than a single dose.

Additional effects from the placing of crystals in the plants were a reduction in the stimulation of adventitious roots characteristic of auxin and also a normal development of shoots on topped plants, instead of the reduced growth typical of plants treated with indolacetic acid applied in lanolin.

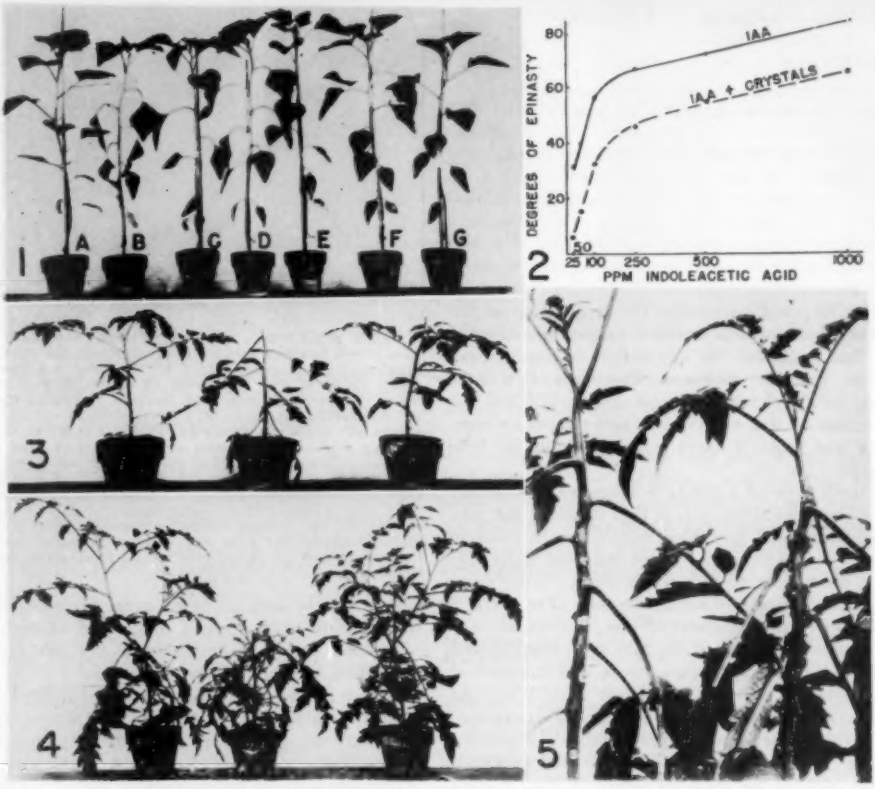
Similar demonstrations of the antiauxin property of the crystalline material were obtained when tomato, *Lycopersicon esculentum* var. Bonny Best, was used as a test plant. Three plants were used in each treatment in triplicated experiments. Crystals were placed in slits in the fourth internode from the base of plants prior to treatment with indolacetic acid either as a water spray of 100 ppm or 1% in lanolin paste. The presence of crystals reduced epinasty by an average of 61% (Fig. 3): reduced adventitious rooting from an average of 86 to 53 roots/plant, and gave near normal suckering of topped plants treated with indolacetic acid (Fig. 4). The presence of crystals in the plants also inhibited the increase in diameter resulting from an application of indolacetic acid. Untreated plants averaged 6.5 mm in diameter, treated plants averaged 9.1 mm, and treated plants with implanted crystals averaged 7.0 mm.

To provide another antiauxin test, tomato plants were inoculated with the crown gall organism *Agro-*

[1] Published by permission of the director of the Agricultural Experiment Station.

[2] Karl Weinke in the laboratory of Mark Stahmann, Department of Biochemistry.

[3] After this paper had been accepted for publication, a paper by M. Ahmed (*Nature*, **170**, 546 [1952]) appeared describing an independent demonstration of mutation of mating type in *S. cerevisiae*.




FIGS. 1–5. Fig. 1, *Xanthium* epinasty. *A*, untreated; *B*, 1000 ppm indolacetic acid; *C*, same as *B* with crystals; *D*, 250 ppm; *E*, same as *D* with crystals; *F*, 100 ppm; *G*, same as *F* with crystals. Fig. 2, *Xanthium*. Graph showing inhibiting effect of crystal injections on epinasty caused by indolacetic acid. Fig. 3, topped tomato var. Bonny Best. Left, untreated; center, 1% IAA in lanolin on cut end (note epinasty); right, same but with crystal injection (epinasty inhibited). Fig. 4, plants similar to Fig. 3, but 18 days later; note shoot inhibition (center) and near normal shoot length where crystals were used (right). Fig. 5, tomato inoculated with the crown gall organism. Right, no crystals used. Note larger galls, marked epinasty, numerous adventitious root initials, and inhibition of stem elongation. Left, inoculated plant but with crystals; auxin effects much inhibited.

*bacterium tumefaciens* (Smith and Town) Conn, strain A6.[3] Plants infected with this bacterium developed large galls, strong leaf epinasty, numerous adventitious roots, and marked cambial activity and made less terminal growth. All the responses, which are typical auxin effects, were related to the high auxin level that arises as the galls develop (*2*). On plants treated with crystals prior to inoculation with the bacteria, early growth of the galls was slower, and leaf epinasty, adventitious rooting, and cambial activity were much inhibited. Nearly normal terminal growth was also made by treated plants (Fig. 5).

The formative effects typical of 2,4-dichlorophenoxyacetic acid, 25–50 ppm, on cocklebur are also inhibited by previous implantation with antiauxin crystals. This reduction in effect of 2,4-D is comparable to the reduced distortion produced by this chemical on plants when they are in flower (*3*).

A record of the effects that active crystals have upon the maturation of the excess tissue produced by stems treated with auxins will be reported elsewhere.

Obviously the warm chloroform-soluble fraction of the extract from flowering plants is highly active physiologically and would appear to exert a marked antiauxin effect.

[3] Inoculations by H. W. Klemmer in association with A. J. Riker, Department of Plant Pathology, and O. N. Allen, Department of Agricultural Bacteriology.

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Manuscript received April 14, 1952.

# Simplified Planigraphic Tube Motion

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The increasing importance of sectional radiography (planigraphy) of the chest and other body areas makes it desirable to extend its availability in clinical practice. Well-designed attachments avoid the high cost and extra space requirement of special equipment and further the application of this valuable diagnostic facility.

The widespread impression that angulation of the tube during its travel is essential to good planigraphy (*1–3*) has restricted the adaptation of many x-ray machines for such purpose. The writer's original planigraph attachment (*4*) was designed to test the justification of this theory. For this purpose a comparison was made of three types of rectilinear tube movement (Fig. 1).

A fourth type of x-ray tube movement, commonly used in some countries (*5*), is that in which the tube both angulates and arcs. This motion was included in the above comparisons, but is not discussed separately since it produced a picture which did not differ from that obtained by merely arcing the tube (Fig. 1 *C*).

To compare the thickness of the planigraphic sections produced by each of the tube movements shown in Fig. 1, a fine copper wire screen was mounted at a 45° angle, on a balsa wood block (Fig. 2 *A*). As a standard for comparison, an ordinary roentgenogram of this copper wire was first obtained (Fig. 2 *B*). Sectional roentgenograms of the wire screen were then made by each of the methods shown in Fig. 1. This amplitude of x-ray tube movement was automatically controlled by an electrically synchronized motor drive. With a 15-in. tube travel all three types of tube movement produced a focal plane thickness of approximately 2 mm (Fig. 2 *C*).

The letters designating the sectional roentgenograms in Fig. 3 correspond to the x-ray tube movements (Fig. 1) by which they were obtained. Taken at the same level through a patient's chest, all three planigrams may be seen to be of equal diagnostic value. Experimental studies and a comparison of such clinical results failed to demonstrate any advantage in angulating the tube during its travel.

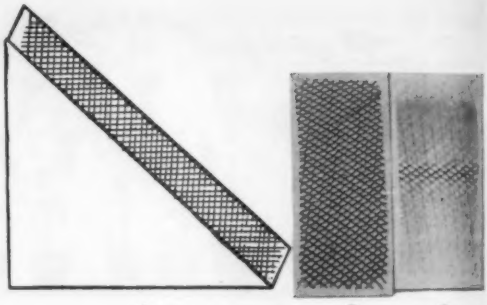



FIG. 2. *A* represents a 45° angle block on which a copper wire screen has been secured to demonstrate the thickness of planigraphic sections obtained by the tube and film movements shown in Fig. 1. At such an angle the wire boxes of which this screen is comprised, measure approximately 1 mm in their vertical diameter. *B*, a conventional roentgen picture of the 45° angle copper screen. It was x-rayed at the same distance and with the same exposure factors used for its subsequent planigraphy. *C*, a planigram of the same copper wire screen obtained with a 15-in. amplitude of planigraphic tube movement and without angulation of the tube (Fig. 1 *B*). The thickness of the resulting planigraphic section, indicated by the sharply focused segment of wire screen, is approximately 2 mm. The uniformly progressive blurring of the copper wire on either side of the focal plane may also be noted.

It may further be noted from Fig. 4 *A* that in customary methods of planigraphy, represented by Fig. 1 *A*, only negligible angulation of the x-ray target occurs during short ranges of tube movement.

The difference in appearance of the cavity in Fig. 3 *C* as compared with 3 *A* and 3 *B* is probably due to some convexity in the plane recorded by arcing the tube (Fig. 1 *C*). This difference, however, is without practical significance, since it is a consistent variation and does not interfere with segmental localization of pulmonary disease or other diagnostic conclusions. Furthermore, the degree of planigraphic curve or convexity which results from merely arcing the x-ray tube is negligible, as shown by additional

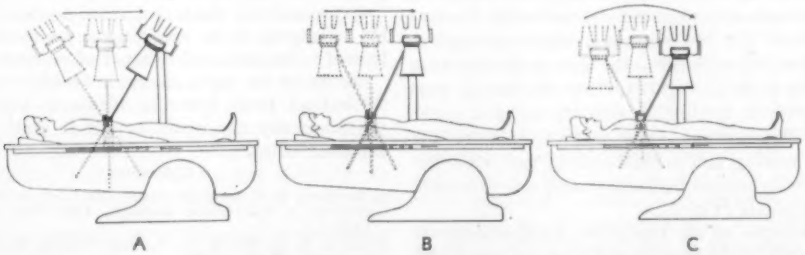
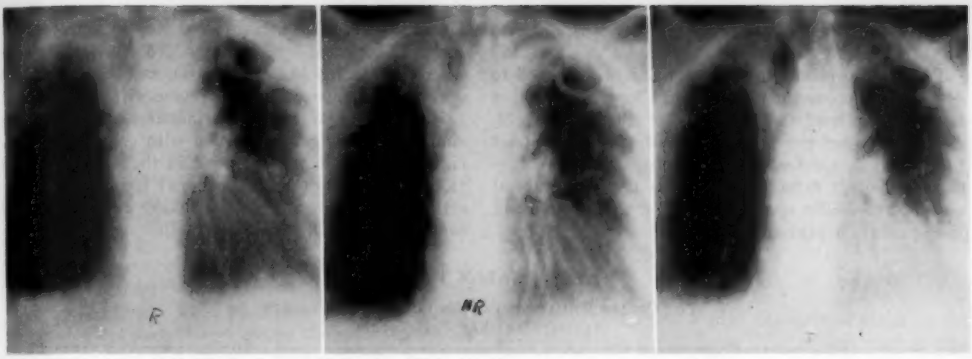
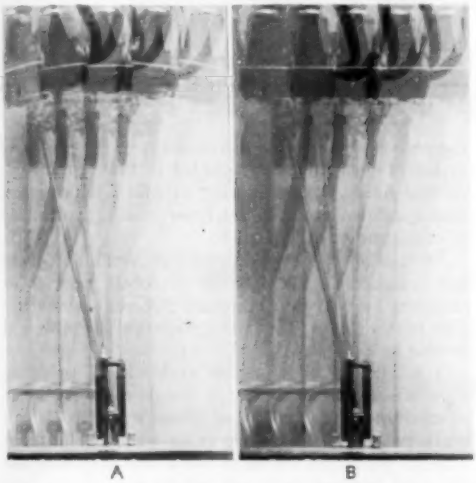



FIG. 1. The three types of rectilinear tube motion compared in this study. *A*, customary planigraphic movement which involves angulation of the x-ray tube. *B*, the simplified planigraphic movement which eliminates tube angulation. This drawing shows extension of the tube travel beyond the range of x-ray film exposure. This must not be construed as evidence of ineffectiveness. The range of x-ray exposure is proved adequate by Fig. 2 *C* and Fig. 3 *B*. Fig. 3 *C* shows a simplified tomographic (arcing) movement, without concomitant angulation of the x-ray tube.



A B C

FIG. 3. These sectional roentgenograms of the chest were taken in the anteroposterior position, 9 cm from the table surface and centered at a 36-in. target to film distance. The tuberculous cavitations shown in the left upper lung offer an opportunity for clinical comparison of the planigraphic movements described. These pictures were obtained by the corresponding x-ray tube motions illustrated in Fig. 1.



A B

FIG. 4. Serial photographs show the slight degree of angulation in x-ray tube portal which occurs during 15 in. of planigraphic movement. *A*, customary type of rectilinear tube movement used in sectional radiography (corresponds to Fig. 1 *A*); *B*, simplified nonangulating x-ray tube motion illustrated for comparison (corresponds to Fig. 1 *B*).

tests with a 14-in. length of "hardware cloth" (½-in. wire mesh). In fact, the arcing tube motion conforms to the contour of many organs such as thorax, lungs, heart, and skull. Since sectional roentgenograms obtained by the simplified tomographic motion (Fig. 1 *C*) have been proved satisfactory, this type of x-ray tube movement can be recommended as a means of extending planigraphy to the Trendelenburg and semiupright positions and as a means of adding stability to some types of x-ray equipment when used for planigraphy in the upright position.

It may be concluded from the above studies that planigraphic movement can be simplified by utilizing short amplitudes of x-ray tube motion and by eliminating x-ray tube angulation, and that this can be accomplished without sacrificing diagnostic quality or the ability to obtain sharp, thin radiographic sections. As a result, many x-ray machines previously considered unsuitable can now be adapted to sectional radiography.

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Manuscript received August 19, 1952.

## Observations on the Cobalt Enhancement of Penicillin Activity Against *Salmonella pullorum*[1, 2]


**Abe Pital,[3] H. J. Stafseth, and E. H. Lucas**

***Departments of Bacteriology and Public Health, and of Horticulture, Michigan State College, East Lansing***


*In vitro* experiments were conducted to evaluate the effectiveness of several antibiotics against *Salmonella pullorum*[4] (the causative agent of pullorum disease in chicks). During the course of routine sensitivity determinations, penicillin at moderately low concentrations was found to exert a slow bactericidal action against this organism. Preliminary *in vivo* studies revealed, however, that penicillin preparations[5] had to be in-

[1] Journal Article No. 1405 of the Michigan Agricultural Experiment Station.

[2] In part, excerpts from thesis of the senior author presented June 1952 to the School of Graduate Studies of Michigan State College, in partial fulfillment of the requirements for the Ph.D. degree.

[3] Present address: Camp Detrick, Frederick, Md.

[4] Strain #89817 (Poultry Pathology Laboratory, Michigan State College) was used in all experiments.

[5] Penicillin G (buffered potassium salt). Supplied through the courtesy of the Upjohn Company, Kalamazoo, Mich.

corporated in feed at relatively high levels in order to be therapeutically effective.

Practical application of these findings appeared to depend on some method that would allow for reduction in penicillin levels without loss of therapeutic efficiency. Previous work by Pratt, Dufrenoy, and Strait (*1–3*) had demonstrated that appropriate concentrations of cobalt definitely enhanced the antibacterial action of penicillin against selected gram-negative and gram-positive organisms.

interest to note that inhibition of respiration by cobalt has been reported by Burk *et al.* (*5*) in *Streptococci, Micrococci,* colon bacteria, yeasts, and in spontaneous mammary adenocarcinomas of mice.

Preliminary *in vivo* experiments have revealed a similar enhancing phenomenon with cobalt and penicillin. Cobalt was administered in the drinking water to day-old chicks (White Leghorn) for 24 hr prior to artificial infection. Ordinary drinking water and a feed containing penicillin were used following infection. An

TABLE 1

THE COBALT ENHANCEMENT (*in vitro*) OF PENICILLIN ACTIVITY AGAINST *S. Pullorum*

| Penicillin (100 u/ml) | | | | | | Cobalt control—no penicillin (0.2 mg/ml) |
|---|---|---|---|---|---|---|
| Series 1 | | Series 2 | | Series 3 | | |
| 2 ml cobalt solution (0.2 mg/ml) | No cobalt | 3 ml cobalt solution (0.2 mg/ml) | No cobalt | 3 ml cobalt solution (0.2 mg/ml) | No cobalt | |
| Zones of inhibition (mm)* | | | | | | |
| 29.2 | 22.0 | 29.1 | 22.4 | 29.1 | 22.8 | 0 0 |

* Each zone reading represents the average value of 8 plate determinations.

The cobalt concentrations employed by the above investigators did not produce any detectable enhancement of penicillin activity against *S. pullorum.* However, with certain modifications of experimental procedure, a pronounced enhancing effect was ultimately demonstrated. Results from these tests are presented in Table 1; they were obtained by utilizing the paper disk technique of Vincent and Vincent (*4*).

No observable inhibitory effects on the test organism were evident at the end of a 24-hr incubation period with the particular concentration of cobalt used. Respiration studies, however, conducted with a Barcroft-Warburg apparatus indicated that cobalt, in a concentration of 0.2 mg/ml, did produce a marked inhibition of oxygen uptake by *S. pullorum.*

It may be postulated that a similar early action of cobalt (applied without penicillin) might have taken place when the organism was grown on plates or in broth, but that its effect was overcome during the later part of a 24-hr incubation period. At the end of this period the organism presented abundant growth. If, however, cobalt was employed together with penicillin, the initial inhibitory effect appeared to be of sufficient magnitude to induce a synergistic phenomenon, as shown in Table 1. Trace amounts of cobalt (0.001 mg/ml) were neither stimulatory nor inhibitory when used alone or in conjunction with penicillin. It is of approximately threefold enhancement of the protective action of penicillin was recorded in those groups receiving cobalt. Chicks serving as cobalt toxicity controls exhibited no ill effects from prolonged drinking of cobalt water.

Pratt *et al.* (*2*) have claimed that incubation of the test organism in the presence of cobalt prior to its exposure to penicillin increased the antibacterial action of the latter. This was confirmed *in vitro* and *in vivo* by the present study.

A detailed account of this work will be published elsewhere. Tests are now in progress to determine whether the concentration of cobalt employed in this study possesses therapeutic value when administered without penicillin. Previous work has indicated that enhanced concentrations of cobalt were in no way protective (*2*). The role of cobalt in a practical program of penicillin therapy is receiving further attention.

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1. PRATT, R., and DUFRENOY, J. *J. Bacteriol.,* **54**, 719 (1947).
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Manuscript received September 22, 1952.

# Comments and Communications

## Terraced Canyons[1]

To a glacialist who has long been a student of Greenland the significance of the great canyons traced by Maurice Ewing and Donald Spurr on the floor of the Atlantic Ocean looms much larger than it does to the general reader. These canyons must have been excavated by rivers that flowed on land surfaces. Ocean rivers, such as the Gulf Stream of the Atlantic or the Japanese Current of the Pacific, do not cut canyons. These canyons were clearly cut by the meltwater from a Greenland glacier, which was several times larger than the present one. Quite a bit of this glacier must have been on land which then surrounded the Greenland of today and which was left unsubmerged because of the withdrawal of the water taken out of the seas to make the glaciers of the Pleistocene.

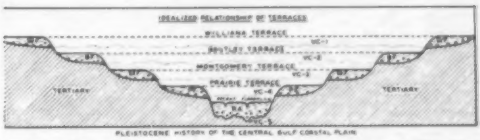
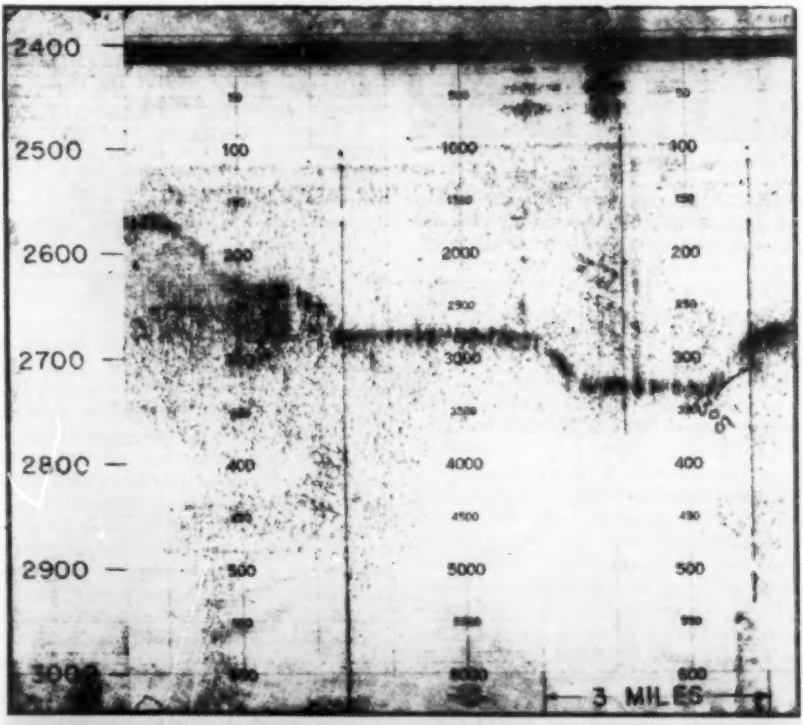



Fig. 21. The four ancestral channels of the Lower Mississippi River, each represented by a pair of terraces, beginning with the earliest, the Nebraskan, at the top (after Fisk).

FIG. 1.

As a student of Greenland I have long expected that these canyons on the floor of the Atlantic would at




**CANYON IS DETECTED** on a depth chart made during one of the tug's passes over it. Chart begins at foothills of mid-Atlantic ridge where water is less than 2,600 fathoms deep (*left*). Tracings show how bottom leveled off at 2,700 fathoms (*center*), dropped abruptly when tug crossed canyon (*right*).

FIG. 2.

[1] *Editorial Note*: This article by William Herbert Hobbs is published posthumously as a tribute to a man whose fertile mind remained active to the time of his death at 88, and whose agile body failed him only a few weeks before this communication was written on his deathbed and submitted on November 11. It was prompted by an article he had read in *Life*, in the issue of October 27. In covering letters he apologized for lack of documentation. SCIENCE hopes to pay further tribute to him in an early article by George D. Hubbard.

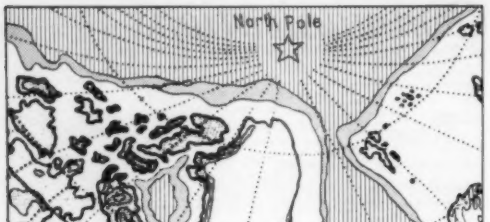



FIG. 3.

some future time be discovered, and just such canyons with matched pairs of large terraces at their sides are found in the lower Mississippi River, in the part south of Cairo known as the Mississippi Embayment (Fig. 1). In 1947 I described these great canyons on the basis of the magnificent monograph by Fisk in a government report. The original maps and sections by Fisk are not easily accessible, but they are reproduced in my recent book (*1*).

An article in *Life* (*2*) shows that the rivers so recently discovered on the floor of the Atlantic had terraces similar to those described by Fisk in the lower Mississippi. This is shown by a comparison of *Life*'s section on page 140 (Fig. 2) with Fig. 1. It can be confidently predicted that when Ewing's section has been extended westward, as it no doubt will be, the uppermost terrace will be found to be the broadest of all. In the lower Mississippi this corresponds to the earliest of the four glaciations, and the river channel of that time was 70 miles across. That on the floor of the Atlantic was formed by a glacier considerably smaller than that of North America and will be considerably narrower.

The terraces of the Mississippi River formed at the same time as those on the floor of the Atlantic will presumably tilt upward toward the north, so that a section made in a higher latitude will be at a higher level. The terraces of the lower Mississippi, of the Great Lakes region, and of the Baltic area all tilt upward at increasingly high angles toward the north.

A comparison with any map of the floor of the Atlantic (such as that of Bartholomew's *Advanced Atlas of Modern Geography* issued in 1950 [Fig. 3]) will show that the canyons described in *Life* follow the lowest levels which meltwater could take flowing on that surface.

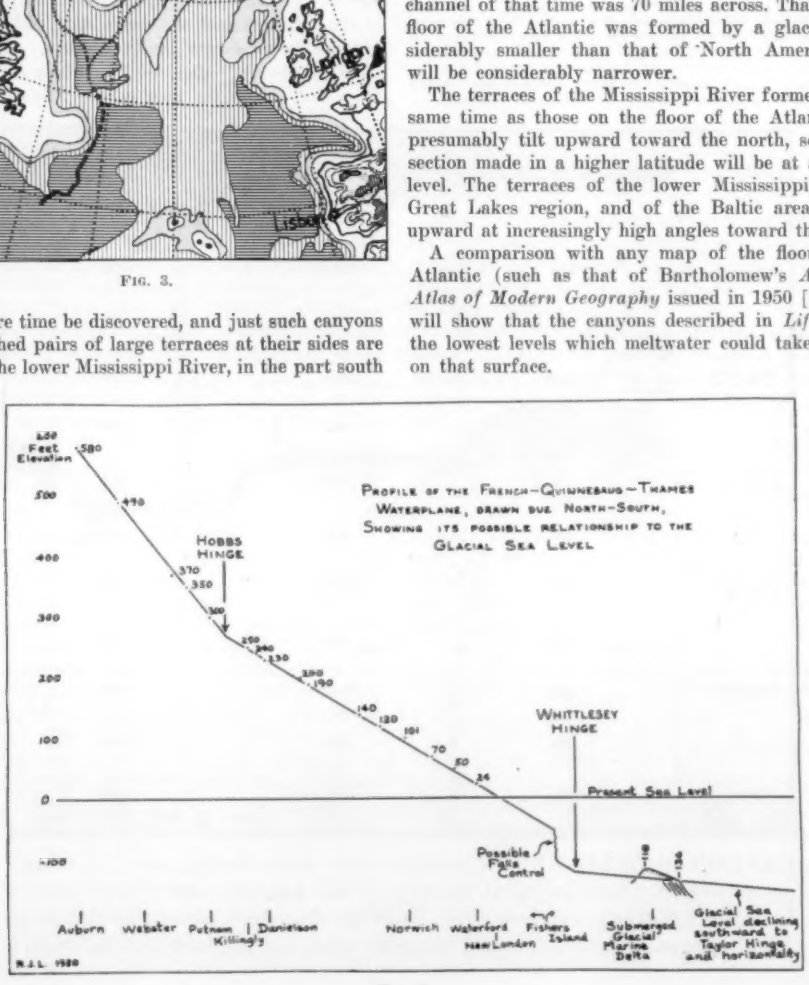



FIG. 4.

It can be confidently predicted also that, when the canyons have all been mapped, there will be found an almost innumerable series leaving the front of the Greenland glacier of that time and flowing into the two forks represented on *Life*'s map. Lougee and Vander Pyl have recently described a line of no vertical movement, which follows the axis of Long Island Sound and continues on the floor of the Atlantic (Fig. 4). South of this axis of neither upward nor downward movement the ocean floor has been sinking at a rapidly increasing rate southward. This has been the main cause of the land bridge which, at the end of the glacial period, joined Europe to America and on which the meltwater of the Greenland glacier took its course and cut the canyons.

WILLIAM HERBERT HOBBS

**References**

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2. *Life*, **33**, (17), 139 (1952).

# *Book Reviews*

***Atomic Energy Levels as Derived from the Analyses of Optical Spectra, 24Cr–41Nb,*** Vol. II. Circ. 467, National Bureau of Standards. Charlotte E. Moore. Washington, D. C.: GPO, 1952. 227 pp. $2.25.

Two years have elapsed since the publication of the first volume of this valuable standard work on atomic energy levels. This is an astonishingly short interval if one considers the enormous amount of work connected with a critical compilation of this kind. Everyone familiar with this type of work is filled with admiration for the author who has carried on this important task with such high efficiency.

This second volume contains the spectroscopic data of the elements chromium to niobium and gives the energy levels of 152 spectra. The arrangement of the tables is the same as in the first volume. The elements are treated in order of increasing atomic number and, for a given element, the spectra follow in the order of increasing ionization stage (Lockyer's symbols). The tables of an element in a given ionization stage are preceded by data concerning ground state configuration, term value of the ground state, ionization potential, explanatory notes, and references. The tables proper contain the data of each level, namely, electron configuration, abbreviated level designation, $J$-values, level with respect to the ground state in $cm^{-1}$, and, if known, Lande's $g$-value. As far as suitable, each level table is followed by an array containing all observed levels and the reference to tables of predicted levels given in Volumes I and II. Two pages of valuable revisions concerning spectra treated in the first volume conclude the impressive work.

K. W. MEISSNER
*Department of Physics, Purdue University*

***Rheumatic Diseases: Diagnosis and Treatment.*** Eugene F. Traut. St. Louis: Mosby, 1952. 942 pp. Illus. $20.00.

A growing interest in the rheumatic diseases is reflected by an increasing number of publications on this subject. A general division of Dr. Traut's text is indicated by the subtitle: "Diagnosis and Treatment." The former constitutes about two thirds and the latter about one third of the book, but there are repetition and overlapping of these subjects in various chapters. Special subjects relating to rheumatic disease are discussed in six chapters contributed separately by other authors.

Uniformity of opinion about rheumatic diseases is perhaps not to be anticipated in the current era of changing concepts. Dr. Traut, in a number of generalized discussions, seems to favor a unitarian concept of rheumatic diseases.

The author discusses his therapeutic experiences in clinical practice and compiles numerous reports from the medical literature. He notes that standardized treatment does not exist and that "improvement obtained by 'psychology' or suggestion need not be condemned." In his opinion, enthusiasm for gold therapy in arthritis is waning. He also has "tried not to display unjustified enthusiasm . . . [for] the exciting new endocrinologic therapy of rheumatic disease." Hence there is limited consideration of this timely aspect of the study and treatment of certain rheumatic diseases.

Dr. Traut regards a stock vaccine "as an indispensable part of my armamentarian" in the therapy of rheumatoid arthritis. He also uses a vaccine for patients convalescing from rheumatic fever, as it has seemed to him that such patients "had decidedly fewer recurrences than those not receiving vaccine."

References are conveniently indicated at the bottom of the pages in most of the chapters. There are charts on differential aspects of some types of articular disease or joints affected. The text is very readable and is free of typographical irregularities. The author has undertaken a comprehensive task in the compilation of a text intended to be "understandable to the medical student, of practical use to the internist and the physician in general practice, and valuable as a reference and source book to the rheumatologist."

HOWARD F. POLLEY
*Department of Rheumatology, Mayo Clinic*

***A Textbook of Arthropod Anatomy.*** R. E. Snodgrass. Ithaca, N. Y.: Comstock Pub.; Cornell Univ. Press, 1952. 363 pp. Illus. $6.00.

In recent years Mr. Snodgrass has concerned himself with comparisons of the anatomy and terminology associated with the anatomy of the various classes of the animal phylum Arthropoda. He states the situation pungently in his preface: "The arthropods are a group of related invertebrates; arthropodists, for the most part, are a group of unrelated vertebrates." The present work is an attempt to correct this situation by unifying treatment of the anatomy of spiders, crabs, insects, etc. The author reaches the conclusion, which he calls "disconcerting," that the facts of arthropod anatomy are not consistent with any of the theories proposed to account for the evolution of the group. Accordingly, rather than expounding on evolution or on any particular phylogenetic scheme, he presents a series of 11 chapters on the anatomy of selected representatives of each of the 11 well-defined classes.

The title is broader than the actual content of the book. Each chapter treats external anatomy in detail, with emphasis on bodily movements and on points thought to be indicative of phylogenetic relationships. For both of these, detailed consideration of the apodemes and of somatic musculature is needed and is given. Relatively detailed treatment is accorded the little-studied question of internal connective tissue—its possible origin, structure, and significance. Mention is also made of the structure of eyes and of invaginations of the epidermis, which form respiratory tubes, genital ducts, etc. The volume is thus more than an external anatomy, and yet it does not treat the internal organ systems such as the alimentary canal and nervous system. It might be characterized as a skeletomuscular anatomy, which analyzes terminology and points of interest to students of phylogeny.

The high caliber, the style of writing, the logical thinking, the personal verification of most of the details presented—even when they are credited to a previous author—and the many superbly drafted illustrations (very few of which are copied) are typical of this author's works.

The book is avowedly for beginning graduate students in invertebrate zoology, entomology, and carcinology, who wish a broad basis for their studies, and for specialists in one group of arthropods, who wish a ready means of comparing details of their particular animals with details as found in other classes of the phylum. It should serve this purpose well. It could also be used as ancillary, albeit advanced, reference in undergraduate courses in invertebrate zoology and insect anatomy.

A. Glenn Richards

*Division of Entomology and Economic Zoology*
*University of Minnesota, St. Paul*

# *Association Affairs*

## Laurentian Hormone Conference

Gregory Pincus

***The Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts***

The Laurentian Hormone Conference of the AAAS will hold its 1953 annual meeting at Mont Tremblant Lodge, Mont Tremblant, Quebec, during the period September 6–11. Interested investigators and specialists in the hormone field may apply for attendance by writing to the Committee on Arrangements, 222 Maple Ave., Shrewsbury, Mass., for application blanks. Since accommodations at the hotel necessarily limit the attendance, only those persons submitting applications can be considered. The application blanks must be received by the committee not later than *May 15* in order to ensure issuance of invitations as soon as possible thereafter.

The following program has been arranged:

I. Nervous System-Hormone Interrelationships
"The Central Nervous System and Stress-induced Eosinopenia," R. W. Porter; "Studies of Brain Metabolism and Electrical Activity in Relation to Adrenocortical Physiology," Hudson Hoagland; "Effects of Hormones on Cerebral Function," D. M. Woodbury.

II. Thyroid Hormone Physiology and Biochemistry
"Triiodothyronine in Relation to Thyroid Physiology," J. Gross and R. Pitt-Rivers; "Metabolic Effects of Thyroid Hormones *in Vitro*," H. A. Lardy and G. Feldott.

III. Comparative Endocrinology
"Endocrine Mechanisms in the Life of Insects," D. Bodenstein; "Hormones Produced by Neurosecretory Cells," Ernst and Berta Scharrer.

IV. Protein Hormones
"The Preparation and Chemistry of Crystalline Insulin," R. G. Romans; "The Chemistry of ACTH," E. E. Hays and W. F. White.

V. The Role of Hormones in Blood and Blood-forming Organs
"Endocrine Factors and Radiation-induced Lymphoid Tumors of Mice," Henry S. Kaplan; "Endocrine Influences upon the Formed Elements of Blood and Blood-forming Organs," Albert S. Gordon.

VI. Aspects of Clinical Endocrinology
"Some Problems Related to Ovarian Function and to Pregnancy," B. Zondek; "Clinical Studies on Electrolyte and Fluid Metabolism," Rolf Luft; "Endocrine-Metabolic Studies in Man," J. W. Conn.

## *Meetings & Conferences*

May 4–5. National Association of State Universities (Annual). Ohio State University, Columbus.
May 4–10. American Association of Cereal Chemists. Buffalo, N. Y.
May 4–6. American Geophysical Union (Annual). Washington, D. C.
May 4–6. American Oil Chemists' Society (Annual). Roosevelt Hotel, New Orleans.
May 4–8. American Psychiatric Association (Annual). Statler Hotel, Los Angeles.
May 5. American Institute of Chemical Engineers Chemical Engineering Symposium, New Jersey Section. Essex House, Newark.
May 7–8. Anthracite Conference (Annual). Lehigh University, Bethlehem, Pa.
May 8–10. Field Conference on Ordovician Stratigraphy and the Physiography of Part of Southeastern Indiana, Department of Geology, Indiana University, and Geological Survey, Indiana Department of Conservation (Annual).
May 11–13. Aero Medical Association (Annual). Biltmore Hotel, Los Angeles.
May 11–13. American Association of Petroleum Geologists (Regional). Tulsa, Okla.
May 14. Conference on Instrumentation in Water, Sewage, and Industrial Waste Treatment. Manhattan College, N. Y.
May 14–15. Society for Applied Spectroscopy (Annual). New York.
May 14–23. International Petroleum Exposition. Tulsa.
May 18–22. National Fire Protection Association (Annual). Palmer House, Chicago.
May 18–22. National Tuberculosis Association (Annual). Los Angeles.
May 18–23. International Congress on Electrothermics (3rd). Paris.
May 20–22. Society of Photographic Engineers (Annual). U. S. Hotel Thayer, West Point, N. Y.
May 22–23. International Syndical Reunion of Gynecologists and Obstetricians. Paris.
May 24–28. Scientific Apparatus Makers Association (Annual). The Greenbrier, White Sulphur Springs, W. Va.
May 25–28. Air Pollution Control Association (Annual). Lord Baltimore Hotel, Baltimore, Md.
May 25–29. Textile Institute (Annual). Llandudno, Wales.
May 25–30. International Hospital Congress. London.
May 25–30. International Seed Testing Association (10th Congress). Dublin.
May 25–31. World Congress of Fertility and Sterility. Henry Hudson Hotel, New York.
May 26–31. World Congress on Fertility and Sterility. New York.
May 28–29. American Rheumatism Association. Waldorf-Astoria, New York.
May 29–31. Field Conference of Pennsylvania Geologists (Annual). Lafayette College, Easton.
May 30–June 1. Society for Investigative Dermatology (Annual). Hotel Belmont Plaza, New York.
June 1–5. American Medical Association (Annual). New York.
June 4–6. Canadian Society of Microbiologists. Ontario Agricultural College, Guelph.
June 5–6. International Congress of Audiology. Leiden.

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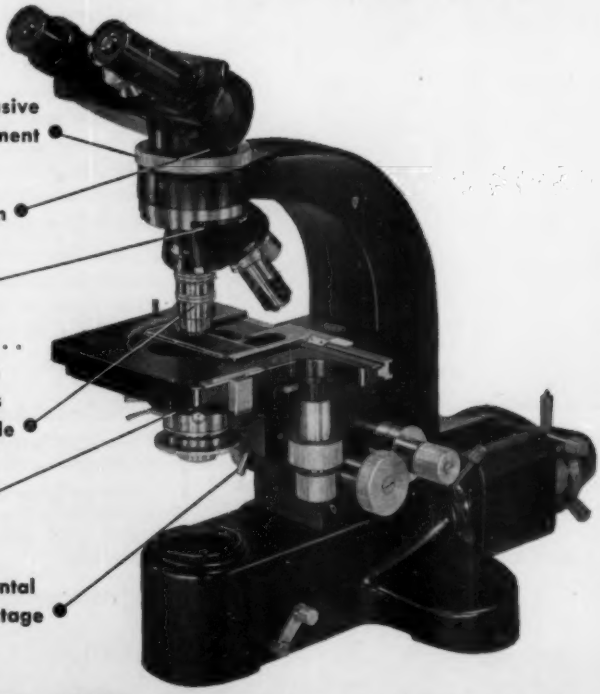

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